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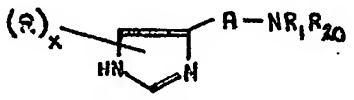
(54) AMINOALKYLIMIDAZOLES AND PROCESSES FOR THEIR PRODUCTION

(71) We, SMITH KLINE & FRENCH LABORATORIES LIMITED, of Mundells, Welwyn Garden City, in the County of Hertford, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to aminoalkylimidazoles, to pharmaceutical compositions comprising aminoalkylimidazoles and to novel processes for their preparation.

The aminoalkylimidazoles with which the present invention is concerned may be represented by the following general formula:



FORMULA I

wherein A is a saturated straight chain of from 1 to 6 carbon atoms, which chain may be substituted by one or more alkyl or aralkyl groups; R is a substituted or unsubstituted alkyl, aryl or aralkyl group; R_1 is hydrogen, alkyl, phenyl, phenylalkyl or imidazolylalkyl; R_{20} is hydrogen, alkyl optionally substituted by halogen, hydroxy, cyano, carboxy, amino or amidino; or —COY wherein Y is $R_{11}O$ or $R_{11}NH$ and R_{11} is a substituted or unsubstituted alkyl, aryl or aralkyl group or an amidino group; and X is 0, 1, 2 or 3, provided that, when X is 0 and R_{20} is hydrogen or an alkyl group containing from 1 to 3 carbon atoms, R_1 may not be hydrogen, benzyl or an alkyl group containing from 1 to 3 carbon atoms and that when R_1 and R_{20} are both hydrogen or alkyl, A is a saturated straight chain of 2 carbon atoms optionally substituted by methyl and X is 1, R may not be methyl, or, except when substituted in the 4(5) position of the ring, phenyl or benzyl.

When one of the nitrogen atoms of the imidazole ring is substituted it will be appreciated that there are two possible isomers as represented in the following formulae IA and IB, wherein A, R, R_1 and R_{20} have the same significance as in formula I and y is 0, 1 or 2.

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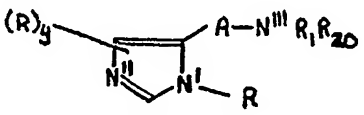
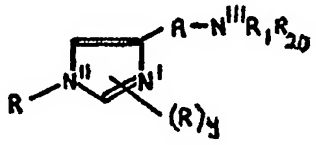


FORMULA I A



FORMULA I B

It will be understood that when R is hydrogen, then formulae IA and IB represent two tautomeric forms of the same compound. The three nitrogen atoms in each of formulae IA and IB have been designated N^{I}, N^{II} and N^{III} and, throughout the following general description, the corresponding nitrogen atoms in the aminoalkylimidazoles described will be referred to in this way.

It will also be understood that in the case of many of the compounds described herein that two or more optical isomers will be possible. A preferred class of compounds of formula I are those wherein R_{2n} is a substituted alkyl group of formula $(CH_2)_nZ$ where n is 1, 2 or 3 and Z is halogen e.g. chloro or bromo, cyano, carboxy, hydroxy, amino or amidino. Within this class, particularly useful compounds are where R_1 is methyl, X is 0 and R_{2n} is 2 - chloroethyl or 2 - bromoethyl.

Further useful classes of compounds of formula I are where X is 0 and R_{2n} is hydrogen; and the compounds of the formulae IC, ID, IE and IF wherein A, R and R_1 have the same significance as in formula I above, each R^1 in formula ID is methyl or benzyl, R^{11} is substituted or unsubstituted aryl or aralkyl and y is 0, 1 or 2.

According to the present invention we also provide processes whereby the compounds of Formula I may be produced. Many of these processes may be used selectively to introduce substituents onto one of the nitrogen atoms present in these compounds while not simultaneously substituting the other two nitrogen atoms. The processes will be described with reference to the accompanying figures 1 to 3 and 5.

Figure 1 relates mainly, but not exclusively, to the production of compounds which are substituted at the N^{II} position in the imidazole ring. It is also restricted to compounds wherein the n of Formula I is 2, i.e. to histamine and its derivatives. In the substances represented by all the formulae in figure 1, R_1 has the same significance as in Formula I, R_2 and R_3 are hydrogen or substituted or unsubstituted alkyl, aryl or aralkyl; and R_1, R_5, R_6 and R_7 which may be the same or different are hydrogen, alkyl or aralkyl. It is however, preferred, because of the necessity to prevent steric hindrance in the reactions, that there should not be too many bulky substituents in the neighbourhood of the site where it is floped to introduce a further substituent. For example, it is preferred in all cases that R_3 should be hydrogen and, at least in the case of the compounds represented by Formulae III to VII, that R_1, R_4, R_5, R_6 and R_7 are hydrogen or lower alkyl. On the other hand it is preferred that R_{1n} (which may be substituted or unsubstituted aralkyl provided that, when R_2, R_3 and one of R_4, R_5, R_6 and R_7 is hydrogen or methyl when the others of R_4, R_5, R_6 and R_7 are hydrogen, R_{1n} may not be benzyl) should be a grouping such that, in going from the substance of Formula VIII to that of Formula IX, substitution will tend to occur to a significantly preferential extent on the N^{II} rather than the N^{I} nitrogen. Suitably, R_{1n} may be phenylethyl.

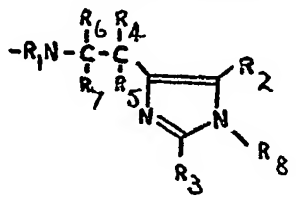
R_8 may be alkyl, aminoalkyl, carboxyalkyl, phenyl, phenylalkyl or imidazolylalkyl provided that, when R_1, R_2 and R_3 are all hydrogen and one of R_4, R_5, R_6 and R_7 is hydrogen or methyl when the others of R_4, R_5, R_6 and R_7 are hydrogen, R_8 may not be methyl, phenyl or benzyl. R_8 is identical to R_9 except that it may be a hydrolysable grouping such as carbethoxy or phthalimido which, on hydrolysis, results in R_9. E (see Formulae VIII and IX) represents the N^{III} nitrogen linked to a suitable protecting group. This protecting group may be monovalent e.g. acetyl or benzoyl or, alternately, it may be divalent an example of the latter being phthaloyl. In the latter case, R_1 in the starting material (Formula II) and product (Formula X) must be hydrogen.

Y (see Formulae VI and VII) is derived from a nucleophilic reagent of formula Y—H such as $R_{11}O$—H or $R_{11}NH$—H wherein R_{11} may be amidino or substituted or unsubstituted alkyl, aryl or aralkyl.

The substance represented by Formula II may be converted to the cyclic urea represented by Formula III by reaction with carbonyl di - imidazole either alone or in a suitable solvent such as dimethylformamide.

Reaction of the cyclic urea (Formula III) with an excess of a compound of formula R_9X, wherein R_9 has the significance stated hereinabove and X is a leaving group such as halogen, either alone of in the presence of a suitable solvent such as dimethylformamide results in the production of the cation represented by Formula IV. Hydrolysis of this e.g. with hot hydrochloric acid yields the N^{II} substituted histamine represented by Formula V. In a preferred example of this process, R_1, R_3, R_4, R_5, R_6 and R_7 are hydrogen. Alternatively, the cation may be reacted with a nucleophile derived from a reagent Y—H,

examples of which, as mentioned above, are $R_{11}OH$ and $R_{11}NH_2$, where R_{11} has the above-mentioned significance, to yield the substance of Formula VII. It has also been found that, under alkaline conditions the substances of Formula IV will give a substance of Formula VII wherein Y has the following structure:—



Very similar reactions may be carried out on the substance of Formula III (which may be considered as the substance of Formula IV wherein R_8 is hydrogen) by treating that substance with a nucleophile derived from a reagent Y—H to yield the substance of Formula VI.

These reactions are suitably carried out on compounds wherein R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are all hydrogen; R_8 is hydrogen or benzyl and Y is methoxy, guanidino, 2 - aminoethylamino or substituted or unsubstituted 2 - (4(s) - imidazolyl) ethylamino.

An alternative route to N^{11} - substituted compounds is illustrated by Formulae VIII, IX and X of figure 1. The N^{111} nitrogen atom is first protected by the formation of a substance of Formula VIII, wherein E has the above-mentioned significance. Where, in the compound of Formula II, R_1 is not hydrogen a monovalent protecting group must be used where in the compound of Formula II R_1 is hydrogen, either a monovalent or a divalent protecting group can be employed. The protecting group may be acetyl but a preferred case is that wherein R_1 is hydrogen and E is N=P, P representing a phthaloyl group, the preferred reagent used to introduce the phthaloyl grouping being N - carbethoxyphthalimide. Treatment of the substance of Formula VIII with $R_{10}X$, where R_{10} has the significance stated hereinabove and X is halogen, in a suitable solvent such as dimethylformamide yields the substance represented by Formula IX which, on hydrolysis, yields the N^{11} - substituted compound represented by Formula X which will of course, as mentioned above be a primary amine (R_1=H) when a divalent protecting group is present in the substances of Formulae VIII and IX. This route may be extended to longer chain aminoalkylimidazoles e.g. to produce 1 - methyl - 4 - (3 - aminopropyl)imidazole.

Figure 2 relates to the production of compounds wherein the N^{111} nitrogen atom of the side chain of the aminoalkylimidazoles is substituted. In the compounds illustrated in figure 2, A has the same significance as in the compound of Formula I; R_2 and R_3 are hydrogen or substituted or unsubstituted alkyl, aryl or aralkyl; R_4, R_5, R_6 and R_7 are hydrogen, alkyl or aralkyl; R_9 is alkyl, aminoalkyl, carboxyalkyl, phenyl, phenylalkyl or imidazolylalkyl; and R_8 is a group which is identical with R_9 or which, on hydrolysis, is converted to R_9, provided that, when R_2 and R_3 are hydrogen, R_9 may not be an alkyl group containing from 1 to 3 carbon atoms or benzyl.

When A is a saturated chain of 2 carbon atoms (n=2), the substance of Formula XI may be converted to the cyclic urea represented by Formula XII in the same way as the compound of Formula II in figure 1 is converted to that of Formula III.

Treatment of this urea (Formula XII) with a base, such as sodium hydride and then with R_8X, wherein R_8 has the significance as stated above and X is halogen results in substitution of the N^{111} nitrogen atom to give the substance represented by Formula XIII. This substance may then be hydrolysed e.g. with hot aqueous alkali yielding the compound of Formula XIV wherein, except in the case where R_8 contains a hydrolysable group such as carbethoxy and R_9 is the hydrolysis product of R_8, R_9 will have the same significance as R_8. Specific examples of compounds which may be subjected to this reaction are those wherein R_3, R_4, R_5, R_6 and R_7 are hydrogen, R_2 is hydrogen, alkyl or phenylalkyl and R_9 is alkyl, phenylalkyl or carbethoxymethyl. Alternatively the substance of Formula XIII may be treated with a reducing agent of the type exemplified by lithium aluminium hydride to yield the tertiary amino compound of Formula XV. The substituent R_{12} will have the same significance as R_8 except in the case where R_8 is reducable under the conditions of the reaction just described when of course R_{12} will be the reduction product. For example, when R_8 is carbethoxymethyl, R_{12} becomes hydroxyethyl. This method is particularly suitable for the production of compounds wherein R_2, R_4, R_5, R_6 and R_7 are hydrogen, R_3 is hydrogen or methyl and R_{12} is 2 - hydroxyethyl or phenylalkyl.

The compound of Formula XI may be converted to the dimethylaminoalkylimidazole compound of Formula XVI wherein, when R_3 is hydrogen, R_2 may not be hydrogen or methyl, by means of the Clarke-Eschweiler reaction (i.e. by reaction with formic acid and formaldehyde) although, when A is such that n is equal to 2, R_2 should not be hydrogen.

Finally, treatment of the compound of Formula XI with an acyl compound such as $(R_{13}CO)_2$ or $R_{13}COX$, wherein R_{13} may be hydrogen or an alkyl, phenyl, phenylalkyl or imidazolylalkyl group provided that, when R_2 and R_3 are both hydrogen, R_{13} may not be hydrogen, methyl, ethyl or phenyl and X is halogen, results in a compound of Formula XVII which may then be reductively con-

verted e.g. by lithium aluminium hydride or diborane to the compound of Formula XVIII.

Two further routes which may be used for the production of N^{111} - substituted aminoalkylimidazoles are illustrated by Formulae XIX to XXIII of figure 2. Both of these routes involve treatment with an amine of Formula $R_{14}R_{15}NH$, wherein R_{14} is alkyl optionally substituted by halogen, hydroxy, cyano, carboxy, amino or amidino and R_{15} is hydrogen, alkyl, phenyl, phenylalkyl or imidazolylalkyl provided that when R_2 and R_3 are both hydrogen, R_{15} may not be hydrogen, an alkyl group containing from 1 to 3 carbon atoms or benzyl and when R_{14} and R_{15} are both alkyl, A is a saturated straight chain of 2 carbon atoms optionally substituted by methyl and one of R_2 and R_3 is hydrogen, R_2 may not be methyl and R_3 may not be methyl, phenyl or benzyl.

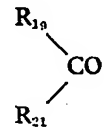
Preferably R_2 and R_3 are hydrogen, R_{14} is methyl or 2 - hydroxyethyl and R_{15} is hydrogen, 2 - hydroxyethyl, 2 - aminoethyl or phenylalkyl.

Treatment of the carbonyl compound of Formula XIX, wherein X is halogen, with $R_{14}R_{15}NH$ yields the substance of Formula XX which may then be reduced e.g. with lithium aluminium hydride or diborane to the substance of Formula XXI whereas treatment of the substance of Formula XXII, wherein A^1 is a saturated chain of from zero to n carbon atoms, n being from 1 to 5, which chain may be unsubstituted or substituted with one or more alkyl or aralkyl groups, R_4 and R_5 are hydrogen, alkyl or aralkyl and X is a suitable leaving group such as halogen, with an amine of formula $R_{14}R_{15}NH$ results in the substance of Formula XXIII. When R_{14} and/or R_{15} is hydrogen and the reaction is carried out in suitable proportions a compound of formula LIII (see figure 5) may be formed.

The substance of formula XXII wherein R_{14} is hydroxyalkyl e.g. 2 - hydroxyethyl may be converted into the substance of that formula wherein R_{14} is chloralkyl or bromoalkyl e.g. 2 - chloroethyl or 2 - bromoethyl by treatment of the hydroxyalkyl compound with thionyl chloride or hydrogen bromide respectively.

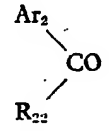
It will be understood that, since many of the compounds illustrated in figure 2 e.g. the compounds of Formulae XIV, XVIII (when A is such that n=2), XXI (when A is such that n=1 and one of R_{14} or R_{15} is hydrogen) and XXIII (when A^1 is such that n=1 and one of R_{14} or R_{15} is hydrogen), fall within the definition of Formula II of figure 1, where R_1 is not hydrogen, these compounds may therefore subsequently be subjected to the reactions with reference to that figure.

In figure 5 there are shown a number of further methods whereby N^{111} - substituted compounds may be produced. The compound of Formula XI may be reacted with a carbonyl compound of Formula



wherein R_{19} and R_{21} are hydrogen, alkyl, phenyl, phenylalkyl or imidazolylalkyl, provided that R_{19} and R_{21} are not both phenyl, phenylalkyl or imidazolylalkyl and that when R_2 and R_3 are both hydrogen, $CHR_{19}R_{21}$ may not be benzyl or an alkyl group containing from 1 to 3 carbon atoms and, when R_{19} and R_{21} are both hydrogen or alkyl, A is a saturated straight chain of 2 carbon atoms optionally substituted by methyl and one of R_2 and R_3 is hydrogen, R_2 may not be methyl and R_3 may not be methyl, phenyl or benzyl to form the Schiff's base of Formula XLVI which may then be reduced directly with, for example, sodium borohydride or catalytically to give the N^{111} - substituted compound of Formula XLVII. In a preferred reaction sequence, R_2 and R_3 are hydrogen, R_{19} is hydrogen or methyl and R_{21} is phenylalkyl. The compound of formula XLVIII may be formed from that of Formula XI by reaction of the latter with acrylonitrile. Treatment of the compound of Formula XI with glycollonitrile in methanol at room temperature yields the compound of Formula IL which may be further converted by way of the corresponding imino - ether to the amidino compound of Formula L. Finally, the compound of Formula LI may be formed from the compound of Formula XI by catalytic hydrogenation of a mixture of the latter with a nitrile of Formula LII when A is Formula XI and A^1 in Formula LII are related by the notation $A=A^1CH_2$.

Figure 5 also demonstrates a reaction for the formation of a compound of Formula LVII wherein the 4(5)cyanomethylimidazole of Formula LIV is first condensed with a carbonyl compound of Formula



wherein Ar_2 is substituted or unsubstituted aryl and R_{22} is hydrogen or alkyl to give the compound of Formula LV which is then first reduced e.g. with sodium amalgam to the compound of formula LVI which on further reduction e.g. with lithium aluminium hydride gives the required compound of Formula LVII, the side chain of which is substituted by a substituted or unsubstituted arylmethyl group and wherein R_2 and R_3 are hydrogen

or substituted or unsubstituted alkyl, aryl or aralkyl, provided that R_2 and R_3 may not both be hydrogen.

Figure 3 relates to the production of compounds which are substituted on the N^1 nitrogen atom of the imidazole ring.

In the compounds illustrated in Figure 3, A has the same significance as in Formula I, E has the same significance as in Formulae VIII and IX of figure 1 and R_2, R_3, R_4, R_5, R_6 and R_7 have the same significance as in the formulae illustrated in figures 1 and 2.

Reaction of the compound represented by Formula XI with a suitable reagent leads to the introduction of a divalent or monovalent protecting group and the formation of the compound represented by Formula XXIV. In the case where E is N=P (see above), the reagent used may conveniently be N - carbethoxyphthalimide. The compound of Formula XXIV may then be converted to the compound of Formula XXV by reaction with QX, wherein X is halogen and Q is a grouping which must (a) form a sufficiently labile bond to the N^{11} nitrogen that it can be relatively easily removed at a subsequent stage of the process and (b) such that it is more likely to attach to the N^{11} nitrogen than to the N^1 nitrogen, for example because it is a more bulky group. A suitable group which satisfies these conditions is the pivaloyloxymethyl group. The N^1 nitrogen atom of the compound represented by Formula XXV can then be substituted by reaction, normally at an elevated temperature, with a substance of Formula $R_{16}X$, wherein X is halogen and R_{16} a substituted or unsubstituted alkyl or aralkyl group, provided that, when R_2 and R_3 are both hydrogen and A is a saturated straight chain of 2 carbon atoms optionally substituted by methyl, R_{16} may not be methyl phenyl or benzyl, to give the cation of Formula XXVI. This cation may then be suitably treated to remove the protecting group from the N^{111} nitrogen, and the group Q from the N^{11} nitrogen. For example, when E is N=P and Q is pivaloyloxymethyl, it may be reacted with ammonia in methanol to remove the pivaloyloxymethyl group yielding the substance of Formula XXVII which may then be hydrolysed in acid to remove the phthaloyl group, P, and yield the N^1 - substituted aminoalkylimidazole of Formula XXVIII. Alternatively, in this specific instance, both the pivaloyloxymethyl and the phthaloyl groups may be removed in a single stage reaction by hydrazinolysis yielding directly the compound of Formula XXVIII. In those cases where A represents a two carbon chain and R_2 is hydrogen, treatment of the compound of Formula XXVIII with formaldehyde yields the so-called "spinaceamine" of Formula XXIX. We have also found, when A and R_2 have these significances in the compound of Formula XXVI and additionally, where Q is such that on hydrolysis it furnishes formaldehyde, then the substances of Formula XXVI can be converted directly to the spinaceamine of Formula XXIX. For example when E in Formula XXVI is N=P, Q is pivaloyloxymethyl, R_2 is hydrogen and A is such that n=2, treatment of the compound of that Formula with hot hydrochloric acid yields a spinaceamine XXIX.

In figure 4 is illustrated a number of processes for the production of 4,5 - disubstituted and 2,4,5 - trisubstituted imidazoles which may then be subjected to the processes illustrated in figures 1, 2 and 3 except, of course, those wherein R_2 should be hydrogen. These substances are therefore useful intermediates in the production of the compounds of Formula I. In the formulae set out in Figure 4, the symbol n represents an integer of from 1 to 6.

In one of these processes the compound of Formula XXX is converted by means of the halogen derivative (Formula XXXI, wherein X is halogen) which is then reacted with formamide to yield the compound of Formula XXXII. Alternatively the same overall process may be achieved by way of the oxime (Formula XXXIII) which may be reductively converted to the corresponding amine (Formula XXXIV) which is then reacted with formamide. The compound of Formula XXXII may be converted to the required aminoalkylimidazoles of Formula XXXV by way of the corresponding hydroxyalkyl, haloalkyl and cyanoalkyl imidazoles. For example, when n=2, and R_2 is substituted or unsubstituted alkyl other than methyl or substituted or unsubstituted aryl or aralkyl other than phenyl or benzyl, the conversion may be accomplished by reduction to the corresponding hydroxymethyl compound, and conversion by way of the halogen derivative to the corresponding nitrile which may then be reduced. In a preferred example of this series of reactions, R_2 is isopropyl or t - butyl.

A second route to the compound of Formula XXXV involves conversion of an acetylenic compound of Formula XXXVI into a compound of Formula XXXVII, wherein E represents an amino group protected by a monovalent or divalent protecting group. When E is N=P this conversion may be accomplished by reaction of the tosyl derivative of the alcohol of Formula XXXVI with potassium phthalimide. The substance of Formula XXXVII may then be oxidised e.g. by potassium permanganate to that of Formula XXXVIII which on reaction with formaldehyde and ammonium acetate yields the compound of Formula XXXIX. Removal of the protecting group from this substance by hydrolysis gives the required compound of Formula XXXV. This process may be particularly exemplified by the compounds

wherein R_2 is ethyl, n - hexyl or phenylpropyl.

The compounds of Formula XL, wherein Ar represents an aryl or substituted aryl group and P^1 represents a divalent protecting group such as P, which can be prepared from the reaction of an omega - haloalkylarylketone and a salt e.g. the potassium salt of the imide of P^1, may be converted to the halogen derivative represented by Formula XLI wherein X is halogen which, on reaction with formamide yields the compound of Formula XLII (wherein R_3 is hydrogen). Use in this reaction instead of formamide of an amidine of formula

$$R_3C(:NH)NH_2$$

wherein R_3 is alkyl, aralkyl or aryl results in the corresponding 2 - substituted imidazole of formula XLII. Hydrolysis of this compound results in the compound of Formula XXXV, wherein R_2=Ar.

The corresponding 2 - substituted imidazoles which are not substituted at the 4 - position may be obtained by reaction of the amidine

$$R_3C(:NH)NH_2$$

with a compound of the formula

$$CH_2XCO(CH_2)_nN=P^1,$$

wherein X, n and P^1 have the same significance as in formula XLI. This compound may be formed from the compound of formula

$$CH_3CO(CH_2)_nN=P^1.$$

Histamine derivatives of Formula XVI may be produced from the corresponding histamine derivative (represented by Formula XLIII) by reaction thereof with an aryl aldehyde or ketone of formula $ArR_{17}CO$, wherein Ar is an aryl or substituted aryl group, and R_{17} is hydrogen or lower alkyl, to give the "spinaceamine" of Formula XLIV which, on catalytic hydrogenolysis e.g. over palladium, may be converted to the required compound of Formula XLV.

The compounds represented by Formula XLV and Formula XXXV, when R_2=Ar, may be hydrogenated to the corresponding saturated cyclic aliphatic hydrocarbon derivative.

The compounds produced by the processes of the present invention are, in many cases, pharmacologically active. They also have utility in being useful as intermediates in the synthesis of pharmacologically active substances.

The pharmacologically active substances are believed to owe their activity to their similarity in structure to histamine, which latter substance is believed to act, in the animal body, through a mechanism which involves combination with certain specific sites known as receptors. Some of the actions of histamine, in fact those which are blocked by drugs of the "antihistamine" type (e.g. mepyramine), are believed to involve a receptor which has been designated by Ash and Schild (Brit. J. Pharmac. Chemother. 1966, *27*, 427) as H-1, but there are other actions of histamine which apparently do not involve the H-1 receptor.

For example stimulation of the secretion of gastric acid from the perfused stomachs of rats by histamine and the action of histamine on the isolated guinea-pig right atrium and rat uterus may be defined as agonist responses at H-2 receptors. Many of the pharmacologically active substances produced by the processes of the present invention are thought to owe their activity to their action at the H-1, H-2 and/or other histamine receptors.

For example 4 - ethyl - 5 - (2 - aminoethyl)imidazole and related N^{111} - methylated derivatives (using the notation of formula Ia) are selective H-2 agonists. Thus their potency relative to histamine on isolated guinea-pig ileum, a histamine H-1 receptor system (using the above definition), is much less than their potency relative to histamine on the stimulation of rat gastric acid secretion, isolated guinea-pig right atrium and rat uterus, which are histamine H-2 receptor systems (using the above definition).

Conversely, certain 2 - substituted histamine derivatives are selective H-1 agonists. Their potency relative to histamine on isolated guinea-pig ileum is much higher than agonist potency on rat gastric secretion, isolated guinea-pig right atrium and isolated rat uterus.

Some other compounds within this invention selectively antagonise the action of histamine at H_1 and/or H_2 receptors. For example 4(5) - (2 - [N - methyl - N - (3 - phenylpropyl]amino)ethylimidazole is a histamine H-1 receptor antagonist (using the previous definition which is shown by its antagonism of histamine on isolated guinea-pig ileum. Examples of compounds which antagonise actions of histamine at H-2 receptors are 4(5) - (N - (2 - bromoethyl) - N - methylamino)ethyl)imidazole and 4(5) - (2 - (N - (2 - chloroethyl) - N - methylamino)ethyl)imidazole.

Accordingly we provide in admixture with suitable pharmaceutically inactive diluents and carriers pharmaceutical compositions which comprise the compounds of formula I as hereinafter claimed in claim 1.

Pharmaceutical compositions comprising 4 - methyl - 5 - (2 - aminoethyl)imidazole, are described and claimed in our co-pending application no. 56235/72 (Serial No. 1341376) which has been divided from the present application.

The pharmaceutical compositions may be in

any form suitable for internal or external administration including tablets, pills, lozenges ointments and injectable solutions and may incorporate one or more further physiologically active compounds in addition to the aminoalkylimidazoles. Compounds which are within the scope of the present invention or which may be used in the pharmaceutical compositions referred to above and intermediates for the preparation thereof are illustrated by the following examples:

Example 1

5 - Oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]-pyrimidine

A stirred mixture of histamine base (22.85 g.) and N,N' - carbonyl di - imidazole (40 g.) was heated in a dry atmosphere to 100° over 1 hour and then at 110—130° for a further 30 minutes. After cooling, the solid cake was ground to a fine powder under ethanol and left to stand at 0° overnight. The mixture was then filtered and the solid washed with ethanol to give 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (24.4 g.), m.p. 219—220°.

Example 2

2 - Methyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium iodide

A stirred mixture of powdered 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (12 g.), methyl iodide (74 g.) and dimethyl formamide (100 ml.) was heated under reflux overnight. After cooling, the mixture was filtered to give the quaternary salt (16.7 g.), m.p. 219—223° (dec.). Addition of ether furnished a second crop (5.3 g.), m.p. 219—223°. An analytical sample (ex methanol/ether) had m.p. 225—227°.

Example 3

1 - Methyl - 4(2 - aminoethyl)imidazole dihydrochloride

A solution of 2 - methyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium iodide (22.8 g.) in 5N hydrochloric acid (200 ml.) was heated under reflux overnight. The solution was evaporated to dryness, the residue dissolved in water (50 ml.) and the aqueous solution added to a solution of excess picric acid in ethanol (500 ml.) to give 1 - methyl - 4 - (2 - aminoethyl)imidazole dipicrate (42.5 g.), m.p. 218—219°. Treatment of this dipicrate with 5N hydrochloric acid and toluene by the standard method gave 1 - methyl - 4 - (2 - aminoethyl)imidazole dihydrochloride (13.5 g.), m.p. 205—207°, after evaporation of the aqueous layer and recrystallisation of the residue from ethanol/ether.

Example 4

2 - Benzyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium bromide

A stirred mixture of benzyl bromide (100 ml.) and powdered 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (10 g.) was heated at 90° for 20 hours. After cooling, the reaction mixture was filtered and the product washed thoroughly with ether to give the pure quaternary salt (22.3 g.), m.p. 224—225°. Other samples, prepared by the same method, melted in the range 214—221°.

Example 5

1 - Benzyl - 4 - (2 - aminoethyl)imidazole dihydrochloride

A solution of 2 - benzyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium bromide (4.5 g.) in 5N hydrochloric acid was heated under reflux overnight. Evaporation of the reaction mixture gave a residual oil which was dissolved in a minimum of water and added to excess saturated potassium carbonate solution. The resulting solution was extracted nine times with chloroform and the combined extracts dried ($MgSO_4$) for 3 hr. Removal of solvent, acidification with ethanolic hydrogen chloride and addition of ether gave the required product (3.68 g.) m.p. 178—180°. Recrystallisation from ethanol afforded the pure product (3.31 g.), m.p. 182—184°.

Example 6

1 - (p - Methoxybenzyl) - 4 - (2 - aminoethyl)imidazole dihydrobromide

Quaternisation of 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (1 g.) with p - methoxybenzyl chloride (10 ml.) by the method described in Example 4 gave 2 - (p - methoxybenzyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium chloride (1.77 g.), m.p. 196—198°, after recrystallisation from acetonitrile/ether.

A solution of 2 - (p - methoxybenzyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]-pyrimidinium chloride (5.3 g.) in 10N sulphuric acid (180 ml.) was heated under reflux overnight. After cooling, the solution was basified with aqueous potassium carbonate, evaporated to dryness and the residue extracted with ethanol. The ethanol extracts were then evaporated to dryness, the residual oil dissolved in chloroform and the solution washed with water and dried ($MgSO_4$). The base obtained after removal of the solvent was dissolved in dry ethanol and acidified with gaseous hydrogen bromide. Addition of tetrahydrofuran gave a hygroscopic solid which furnished 1 - p - methoxybenzyl - 4(2 - aminoethyl)-imidazole dihydrobromide (3.46 g.), m.p. 87—90°, after recrystallisation from isopropanol/tetrahydrofuran, and filtration in a dry atmosphere.

Example 7

1 - (p - Hydroxybenzyl) - 4 - (2 - aminoethyl)imidazole dihydrobromide

A solution of 1 - (p - methoxybenzyl) - 4 - (2 - aminoethyl)imidazole dihydrobromide (1.57 g.) in 48% hydrobromic acid (25 ml.)

was heated under reflux overnight. After removal of the solvent, the residue was dissolved in hot ethanol and filtered through charcoal. Further evaporation and addition of isopropanol/ether gave the crude product (1.21 g.), m.p. 180—185°. After several recrystallisations from isopropanol/ether chromatographically pure title compound (as its dihydrobromide), m.p. 182—184° was obtained.

Example 8

1 - Butyl - 4(2 - aminoethyl)imidazole dihydrochloride

A stirred mixture of 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (3 g.), n - butyl bromide (10 ml.) and dimethyl formamide (20 ml.) was heated at 110° overnight. After evaporation the residue was recrystallised from isopropanol/ether to give 2 - butyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium bromide (3.9 g.), m.p. 146—148°.

This quaternary salt (3 g.) was hydrolysed by the method described in Example 5. The crude product was recrystallised from isopropanol/ether to give 1 - butyl - 4(2 - aminoethyl)imidazole dihydrochloride (2.02 g.), m.p. 110—112°.

Example 9

1 - p - Nitrobenzyl - 4 - (2 - aminoethyl)-imidazole dihydrochloride

Quaternization of 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (8.2 g.) with p - nitrobenzyl bromide (19.4 g.) by the method described in Example 4 gave, after filtration of the cool reaction mixture, 2 - (p - nitrobenzyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium bromide (15.9 g.), m.p. 243—244°.

This quaternary salt (17.9 g.) was converted to the required histamine derivative by the method described in Example 5. Recrystallisation of the crude product from ethanol/ether gave 1 - (p - nitrobenzyl) - 4 - (2 - aminoethyl)imidazole dihydrochloride (7.6 g.), m.p. 168—171°.

Example 10

1,4 - Bis - (2 - aminoethyl)imidazole trihydrochloride

A stirred mixture of 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (15.1 g.), 2 - bromoethylphthalimide (70 g.) and dimethylformamide (200 ml.) was heated at 105° overnight. After cooling, the reaction mixture was filtered and the product washed with tetrahydrofuran to give 5 - oxo - 2 - (2 - phthalimidoethyl) - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium bromide (27.2 g.), 246—248°. An analytical sample (ex methanol) had m.p. 250.5—251.5°. This quaternary salt (27.2 g.) was hydrolysed by the method described in Example 3 to give, after filtration of the cold reaction mixture, 1,4 - bis - (2 - aminoethyl)imidazole tripicrate (27.3 g.), m.p. 214.5—215.5°. Treatment of this picrate with hydrochloric acid and toluene by the usual procedure gave 1,4 - bis - (2 - aminoethyl)imidazole trihydrochloride (8 g.), m.p. 226—229°. Recrystallisation from methanol/ether furnished an analytical sample, m.p. 224—227°.

Example 11

1 - Carboxymethyl - 4 - (2 - aminoethyl)-imidazole dihydrochloride

A stirred mixture of 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (2.7 g.), ethyl chloroacetate (12.3 g.) and dimethylformamide (20 ml.) was heated at 105° for 1 hr. A further 20 ml. of ethyl chloroacetate was added, the solution cooled, filtered and the product washed with ethyl chloroacetate and tetrahydrofuran to give 2 - ethoxycarbonylmethyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium chloride (4 g.), m.p. 170—171° (dec.). Recrystallisation from isopropanol gave an analytical sample, m.p. 170—171°. A solution of this quaternary salt (2.1 g.) in 5N hydrochloric acid was heated under reflux overnight to give, after evaporation and recrystallisation of the residue from ethanol, 1 - carboxymethyl - 4 - (2 - aminoethyl)imidazole dihydrochloride (1.44 g.), m.p. 183—185°.

Example 12

1 - (Naphth - 1 - ylmethyl) - 4 - (2 - aminoethyl)imidazole dihydrochloride

Quaternization of 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (2.74 g.) with 1 - chloromethylnapthalene (17.7 g.) in dimethylformamide (20 ml.) by the method described in Example 10 gave, after filtration of the cool reaction mixture, 2 - (naphth - 1 - yl - methyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium chloride (4.5 g.), m.p. 192—193°. An analytical sample, recrystallised from ethanol/ether, had m.p. 195—196°.

Hydrolysis of this quaternary salt (3.47 g.) by the method described in Example 11 gave 1 - (naphth - 1 - yl - methyl) - 4 - (2 - aminoethyl)imidazole dihydrochloride (3.57 g.) m.p. 246—248°, after evaporation of the reaction mixture and addition of tetrahydrofuran. Traces of histamine were removed by conversion to the base, extraction and re-acidification as described for Example 5 to give 2.47 g., m.p. 247—249°. An analytical sample (ex ethanol/methanol) had m.p. 248—250°.

Example 13

4(5) - (2 - Phthalimidoethyl)imidazole

Sodium carbonate (21.2 g.) was added to a solution of histamine dihydrochloride (18.4 g.) in water (300 ml.) with cooling and

vigorous stirring. Finely ground N - carbethoxyphthalimide (25 g.) was then added in small portions and stirring was continued for 1 hour after complete addition. The solid present was collected and recrystallised from aqueous ethanol affording 4(5) - (2 - phthalimidoethyl)imidazole (22.7 g.), m.p. 188—190°.

Example 14

1 - Benzyl - 4 - (2 - aminoethyl)imidazole dihydrochloride

Benzyl chloride (2.33 g.) was added slowly with stirring to a warm solution of 4(5) - (2 - phthalimidoethyl)imidazole (4.0 g.) and triethylamine (1.84 g.) in dimethyl formamide (20 ml.). The mixture was subsequently heated at steam bath temperature for 2½ hours and then concentrated under reduced pressure. The residue was triturated with water and extracted with chloroform. Concentration of the chloroform extracts, followed by acidification with a solution of hydrogen chloride in isopropyl alcohol afforded 1 - benzyl - 4(2 - phthalimidoethyl)imidazole hydrochloride (2.0 g.), m.p. 227—230°. Recrystallisation from n - butanol afforded 1.65 g., m.p. 236—238°. An analytical sample (ex n - butanol) had m.p. 242—243°.

Hydrolysis of the phthalimide derivative (1.55 g.) with 6N hydrochloric acid for 6 hours yielded 1 - benzyl - 4 - (2 - aminoethyl)imidazole dihydrochloride (0.95 g.), m.p. 182—184°. Recrystallisation from n - butanol - ether furnished 0.82 g., m.p. 182—184°.

Example 15

1 - (2 - Phenylethyl) - 4 - (2 - aminoethyl)-imidazole dihydrochloride

4(5) - (2 - Phthalimidoethyl)imidazole (8.13 g.) was reacted with 2 - phenylethyl bromide (6.68 g.) and triethylamine (3.68 g.) by the method described in Example 14. The crude product hydrochloride (7.4 g.) was converted to the base (5.7 g.) and purified by chromatography on silica gel SG32. Acidification with hydrogen chloride followed by recrystallisation from isopropyl alcohol afforded 1 - (2 - phenylethyl) - 4 - (2 - phthalimidoethyl)-imidazole hydrochloride (1.20 g.), m.p. 190—191°.

Hydrolysis of the phthalimido derivative (1.31 g.) with 6N hydrochloric acid for 17 hours yielded 1 - (2 - phenylethyl) - 4 - (2 - aminoethyl)imidazole dihydrochloride (0.82 g.), m.p. 200—201.5°.

Example 16

4(5) - (2 - n - Butylaminoethyl)imidazole dihydrochloride

A solution of 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (1.14 g.) in dry dimethylformamide (25 ml.) was added to a stirred suspension of sodium hydride (0.5 g. 40%) in dimethylformamide (10 ml.). After stirring under nitrogen at room temperature for 45 min., a solution of n - butyl bromide (1.14 g.) in dimethylformamide (15 ml.) was then added rapidly and the mixture stirred for a further 24 hr., filtered and, evaporated to dryness. The residue was dissolved in chloroform and the solution filtered and evaporated to dryness. Addition of isopropanolic hydrogen chloride and ether gave a solid precipitate which was recrystallised from isopropanol/ether to give 6 - n - butyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]-pyrimidine hydrochloride (1.28 g.), m.p. 155—157°.

A solution of the above hydrochloride (1.24 g.) in aqueous 5N potassium hydroxide 25 ml.) was heated under reflux overnight. The reaction mixture was acidified with concentrated hydrochloric acid, filtered, the filtrate evaporated to dryness and the residue extracted with hot ethanol. This solution was evaporated to dryness and the residue chromatographed on a cationic exchange resin (H^+ form) to give, after evaporation and recrystallisation from butanol, 4(5) - (2 - n - butylaminoethyl)-imidazole dihydrochloride (0.73 g.), m.p. 206—208°.

Example 17

4(5) - (2 - n - Propylaminoethyl)imidazole dihydrochloride

5 - Oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (2.58 g.) was reacted with sodium hydride (1.13 g. 40%) and n - propyl bromide (2.31 g.) by the method described in Example 16 to give 5 - oxo - 6 - n - propyl - 5,6,7,8 - tetrahydroimidazo[1,5 - c]-pyrimidine hydrochloride (1.5 g.), m.p. 152—154° after recrystallisation from ethanol/ether. This hydrochloride was hydrolysed with aqueous potassium hydroxide by the method described in Example 16. Addition of hydrochloric acid, evaporation to dryness, and extraction with ethanol gave, after concentration and addition of ether 4(5) - (2 - n - propylaminoethyl)imidazole dihydrochloride (1.94 g.) m.p. 184—185°.

Example 18

4(5) - (2 - n - Hexylaminoethyl)imidazole dihydrochloride

5 - Oxo - 5,6,7,8 - tetrahydroimidazo-[1,5 - c]pyrimidine (1.14 g.) was reacted with sodium hydride (0.75 g. 40%) and n - hexyl bromide (1.38 g.) by the method described in Example 16. The hydrochloride of 6 - n - hexyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo-[1,5 - c]pyrimidine, which was precipitated as a crude oil with ether, was hydrolysed with aqueous potassium hydroxide as described previously. Acidification and extraction of the hydrochloride with ethanol, as described in Example 16, gave the crude hydrated hydrochloride (1.48 g.) m.p. 160—170°, on addi-

tion of ether to the ethanol solution. Purification by ion exchange chromatography gave, after evaporation and recrystallisation from n - butanol, 4(5) - (2 - n - hexylaminoethyl)-imidazole dihydrochloride, m.p. 230—232°.

Example 19

5 - Oxo - 6 - (3 - phenylpropyl) - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine hydrochloride

5 - Oxo - 5,6,7,8 - tetrahydroimidazo-[1,5 - c]pyrimidine (4 g.) was reacted with sodium hydride (1.75 g., 40%) and 3 - phenylpropyl bromide (5.8 g.) by the method described in Example 16, to give, after work-up, the required hydrochloride (3.65 g.), m.p. 167—169°.

Example 20

4(5) - [2 - (3 - Phenylpropyl)aminoethyl]-imidazole dihydrochloride

5 - oxo - 6 - (3 - Phenylpropyl) - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine hydrochloride (0.98 g.) was hydrolysed with aqueous potassium hydroxide by the method described in Example 16. Addition of hydrochloric acid followed by evaporation and extraction of the residue with ethanol gave 4(5) - [2 - (3 - phenylpropyl)aminoethyl]-imidazole dihydrochloride (0.78 g.), m.p. 205—207°. An analytical sample (ex isopropanol) had m.p. 209—211°.

Example 21

4(5) - [2 - (N - Methyl - N - (3 - phenylpropyl)amino)ethyl]imidazole dihydrobromide

5 - Oxo - 6 - (3 - phenylpropyl) - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine hydrochloride (3.1 g.) was converted to the base by addition of aqueous potassium carbonate, extraction with chloroform and evaporation to dryness. A solution of this base in tetrahydrofuran (100 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (1.48 g.) in tetrahydrofuran (20 ml.) and the solution heated under reflux for 2 hr. After cooling, water was added carefully, the mixture filtered and the residue washed with tetrahydrofuran and ethanol. The filtrate was evaporated to dryness, the residue extracted with chloroform and the extracts washed with water, dried ($MgSO_4$), and filtered. After removal of the chloroform, hydrogen bromide gas was passed into a solution of the crude base in ethanol to give the dihydrobromide of the required product. Recrystallisation from isopropanol/tetrahydrofuran gave 2.96 g. m.p. 127—129°.

Example 22

5 - Oxo - 6(2 - ethoxycarbonylmethyl) 5,6,7,8 tetrahydroimidazo[1,5 - c]pyrimidine hydrochloride

5 - Oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (6.23 g.) was reacted with sodium hydride (2.72 g. 40%) and ethyl chloroacetate (5.56 g.) by the method described in Example 16, to give the required hydrochloride (10.25 g.) m.p. 161—163°. Recrystallisation from ethanol/ether gave an analytical sample, m.p. 173—175°.

Example 23

4(5) - [2 - [N - (2 - Hydroxyethyl) - N - methyl]aminoethyl]imidazole dihydrochloride

A solution of sodium (0.69 g.) in ethanol (70 ml.) was added to a solution of 5 - oxo - 6 - (2 - ethoxycarbonylmethyl) - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine hydrochloride (7.8 g.) in ethanol (200 ml.) and the mixture filtered. After evaporation to dryness the crude base was reduced with lithium aluminium hydride (5.69 g.) by the method described in Example 21. After decomposition of the excess lithium aluminium hydride, the mixture was filtered, evaporated to dryness and the residue extracted with hot ethanol and filtered through charcoal. The filtrate was concentrated, acidified with ethanolic hydrogen chloride and ether added to give the required dihydrochloride (6.3 g.) m.p. 161.5—162.5°. Recrystallisation from ethanol/ether gave 5.2 g. of pure product m.p. 164.5—165.5°.

Example 24

4(5) - (2 - Methylaminoethyl)imidazole dihydrochloride

Histamine base (4.4 g.) was dissolved in chloroform (40 ml.) and chloral (6.6 g.) was added dropwise. After stirring at room temperature for 1 hour, the solid present was filtered off, dried and recrystallised from methanol - ether in the cold. Crystals of histamine monohydrochloride which deposited were removed by filtration. From the filtrate was obtained a solid (4.0 g.) which was recrystallised twice from isopropyl alcohol - ether, yielding 4(5) - (2 - formamidoethyl)-imidazole (2.3 g.), m.p. 99—102°.

4(5) - (2 - Formamidoethyl)imidazole (2.8 g.) was added gradually to a slurry of lithium aluminium hydride (2.0 g.) in anhydrous tetrahydrofuran. The resulting suspension was heated under reflux for 3 hours. After cooling, wet ether was added, followed by water (20 ml.) and 5N hydrochloric acid (50 ml.). Following extraction with ether, the aqueous solution was evaporated to dryness and the residue was extracted with ethanol. The addition of ether to the ethanol extracts precipitated a solid which was recrystallised from ethanol - ether, yielding 4(5) - (2 - methylaminoethyl)imidazole dihydrochloride (2.1 g.), m.p. 177—179°.

Example 25

4(5) - (2 - Ethylaminoethyl)imidazole dihydrochloride

(i) 4(5) - (2 - Acetamidoethyl)imidazole (2.5 g.) was reacted with lithium aluminium

hydride (1.0 g.) according to the method described in Example 24. The product was recrystallised three times from ethanol - ether yielding 4(5) - (2 - ethylaminoethyl)imidazole dihydrochloride, m.p. 169—170°.

(iii) Diborane, generated from sodium borohydride (6.8 g.) and boron trifluoride etherate (51 g.) in dry diethyleneglycol dimethyl ether (180 ml.) in the usual way, was bubbled into a stirred suspension of 4(5) - (2 - acetamidoethyl)imidazole (6.0 g.) in tetrahydrofuran with external cooling. When the passage of diborane was complete, the reaction mixture was heated under reflux for 36 hours. The resultant clear solution was cooled in an ice-bath and 6N hydrochloric acid (60 ml.) was added cautiously. The mixture was heated under reflux for 2 hours and then evaporated to dryness. The residue was dissolved in a little water and treated with ion-exchange resin IRA 401 (OH^-). A large volume of gas was evolved during this process and dissolved gas was removed in vacuum. The aqueous solution was added to ion-exchange resin IRC 50 (H^+) and eluted with hydrochloric acid. Concentration of the eluent gave a solid which was recrystallised several times from ethanol - ethyl acetate yielding 4(5) - (2 - ethylaminoethyl)imidazole dihydrochloride, m.p. 168—169°.

Example 26

4(5) - (2 - Benzylaminoethyl)imidazole dihydrochloride

4(5) - (2 - Benzamidoethyl)imidazole (2.0 g.) was reacted with lithium aluminium hydride (0.35 g.) according to the method described in Example 24. The product was recrystallised from ethanol - ether yielding 4(5) - (2 - benzylaminoethyl)imidazole dihydrochloride (2.5 g.), m.p. 225—227°.

Example 27

4(5) - (2 - Bromoethyl)imidazole hydrobromide

A solution of 4(5) - (2 - hydroxyethyl)-imidazole (40.0 g.) in 50% aqueous hydrobromic acid (700 ml.) containing a few drops of hydriodic acid was boiled under reflux for 3 days. Following concentration under reduced pressure, the residue was dissolved in water, treated with charcoal and the solution concentrated. The residue was recrystallised from ethanol - ether, affording 4(5) - (2 - bromoethyl)imidazole hydrobromide (65 g.), m.p. 147—149°.

Example 28

4(5) - (2 - tert - Butylaminoethyl)imidazole dihydrochloride

A solution of 4(5) - (2 - bromoethyl)-imidazole hydrobromide (5.1 g.) and tert - butylamine (7.3 g.) in dimethylformamide (50 ml.) was heated at steam bath temperature for 17 hours. The solvent was removed under reduced pressure and the residue was treated with excess aqueous potassium carbonate. Following evaporation to dryness the residue was extracted with isopropyl alcohol and the extracts were concentrated and treated with ethanolic hydrogen chloride. The solid obtained (2.9 g.) was twice recrystallised from methanol - isopropyl alcohol - ether, yielding 4(5) - (2 - *tert* - butylaminoethyl)imidazole dihydrochloride m.p. 286—288°.

Example 29

4(5) - [2 - N - (2 - Aminoethyl)aminoethyl]imidazole trihydrochloride

A solution of 4(5) - (2 - chloroethyl)-imidazole hydrochloride (2 g.) in ethanol (20 ml.) was added rapidly to ethylenediamine (20 ml.) and the mixture left to stand overnight. After heating for 1 hour on a steam-bath a solution of sodium hydroxide (1 g.) in water (10 ml.) was added and the mixture evaporated to dryness under reduced pressure to remove unchanged ethylenediamine. Ethanol was then added, the mixture filtered and the filtrate acidified with ethanolic hydrogen chloride. The precipitated oil was dissolved in methanol and the solution filtered hot to remove ethylenediamine hydrochloride. After cooling the crude product was filtered off and recrystallised twice from methanol to give 4(5) - [2 - N - (2 - aminoethyl)aminoethyl]imidazole dihydrochloride (1.07 g.), m.p. 207—209°.

Example 30

4(5) - [2 - N - (2 - Hydroxyethyl)aminoethyl]imidazole dihydrochloride

Reaction of 4(5) - (2 - chloroethyl)-imidazole hydrochloride (2 g.) with ethanolamine (30 ml.) by the method described in Example 29 gave 4(5) - [2 - N - (2 - hydroxyethyl)aminoethyl]imidazole dipicrate (5.8 g.), m.p. 204—206° after addition of picric acid to the crude hydrochloride first obtained. Recrystallisation from ethanol/water gave 5.56 g., m.p. 205—207°.

Conversion of the dipicrate to the base, followed by the addition of an ethanolic solution of maleic acid and then tetrahydrofuran gave the dimaleate, m.p. 111—113°.

Example 31

4(5) - [N - Methyl - N(2 - hydroxyethyl)-aminomethyl]imidazole dihydrochloride

4(5) - Chloromethylimidazole hydrochloride (7.65 g.) in dimethylsulphoxide (50 ml.) was slowly added to a solution of sodium 2 - methylaminoethoxide (0.1 moles) in dimethylsulphoxide (200 ml.) and the stirred mixture was heated at 60° for one hour, then cooled, filtered and evaporated. The resulting residue was added to one litre of a hot saturated aqueous solution of picric acid. The resulting crystalline precipitate was crystal-

lised from water to yield 20.4 g. of 4(5) - [N - methyl - N(2 - hydroxyethyl)aminomethyl]imidazole dipicrate as orange needles of h.p. 212—214°. Conversion into the dihydrochloride in the normal manner gave hygroscopic crystals of m.p. 118—120° (from ethanol).

Example 32

4(5) - [N - (2 - Hydroxyethyl)aminomethyl]imidazole dihydrochloride

A mixture of 4(5) - chloromethylimidazole hydrochloride (7.65 g.) and excess of 2 - aminoethanol (30.6 g.) was heated for one hour at 50°. The excess aminoethanol was distilled out under reduced pressure and the residue was dissolved in water and added to a hot saturated solution of picric acid in one litre of water to precipitate an oily picrate. The supernatant liquid, after being separated, deposited a crystalline picrate. The latter was crystallised from water (600 ml.) to furnish 4(5) - [N - (2 - hydroxyethyl)aminomethyl]imidazole dipicrate as orange needles. Recrystallisation gave a pure sample of m.p. 216—218°. Conversion into the dihydrochloride in the normal manner gave hygroscopic needles of m.p. 154—155° (from ethanol).

Example 33

4(5) - [N - (2 - Aminoethyl)aminomethyl]-imidazole trihydrochloride

Ethylenediamine (26.4 g.) was added slowly to a solution of 4(5) - chloromethylimidazole hydrochloride (5 g.) in anhydrous ethanol (60 ml.) and the mixture was heated at 55° for one hour. It was then concentrated and finally warmed in vacuo to remove much of the unchanged ethylenediamine. The residue was dissolved in warm ethanol and the solution was acidified with anhydrous hydrogen chloride and then cooled. The resulting white solid which crystallised out was collected by filtration and then dissolved in hot 50% aqueous ethanol, this solution initially deposited crystals of ethylenediamine dihydrochloride (these were removed by filtration) and later deposited crystals of 4(5) - [N - (2 - aminoethyl)aminomethyl]-imidazole trihydrochloride. The latter was recrystallised several times from aqueous ethanol to afford analytically pure material of m.p. 218—220°.

Example 34

4(5) - (2 - Phenylaminoethyl)imidazole dimaleate

4(5) - Imidazolylacetyl chloride (6.6 g.) was added gradually to rapidly stirred aniline (20 ml.) at room temperature and the mixture was set aside for 17 hours. After addition to water, excess aniline was removed by ether extraction and the aqueous solution was passed through a column of IRA-401 (OH^-) resin. From the eluate was obtained N - phenyl - 4(5) - imidazolyl acetanilide as a crystalline solid (4.4 g.), m.p. 180—184° which was collected and washed with ether. An analytical sample (ex water) had m.p. 191—192°.

N - Phenyl - 4(5) - imidazolyl acetanilide (4 g.) was suspended in anhydrous tetrahydrofuran and a solution of diborane in tetrahydrofuran (175 ml. 1M) was added slowly with cooling. When the effervescence had subsided, the mixture was heated under reflux for 6 hours. The mixture was set aside at room temperature for 17 hours and then cooled during the gradual addition of 5N hydrochloric acid (100 ml.). The mixture was heated under reflux for 1 hour and then evaporated to dryness. The residue was basified with sodium hydroxide and extracted with ether. The ether extracts were concentrated to afford the product in the form of its base as an oil (3.0 g.). A crystalline salt was obtained by treatment of the base (1.2 g.) with maleic acid (1.6 g.) in ethanol (25 ml.) followed by the addition of ether. Recrystallisation from ethanol afforded 4(5) - 2 - (phenylaminoethyl)-imidazole dimaleate (1.5 g.), m.p. 131—132°.

Example 35

4(5) - (2 - [N - (1 - phenyl - 2 - n - propyl)-amino]ethyl)imidazole dimaleate

4(5) - Imidazolylacetyl chloride (10 g.) was reacted with dl - amphetamine (25 g.) in toluene at room temperature for 5 days. Concentration gave an oil which was dissolved in methanol and passed through a column of IRA-400 (OH^-) presoaked in methanol. Concentration of the eluate followed by the addition of petroleum ether gave a solid (8.2 g.), m.p. 149°. Recrystallisation from aqueous acetone afforded 4(5) - imidazolyl - N - (1 - phenyl - 2 - n - propyl)acetamide (5.0 g.), m.p. 157—158°.

A sample (1 g.) of this material was reduced with diborane internally generated from boron trifluoride etherate (2.33 g.), and sodium borohydride (0.47 g.) in diethylene glycol dimethyl ether in the usual way. The product was isolated as the base by the method described in Example 34 and converted to the dimaleate (0.72 g.) with maleic acid (1.9 g.) in ethanol. Recrystallisation from ethanol - diisopropyl ether afforded 4(5) - (2 - [N - (1 - phenyl - 2 - n - propyl)amino]ethyl)imidazole dimaleate (0.52 g.), m.p. 155°.

Example 36

4(5) - [2 - (N - (3 - Phenylpropyl)amino) - 1,1 - dimethylethyl]imidazole dihydrochloride

4(5) - Imidazolyl - 2,2 - dimethylacetic acid hydrochloride (11.8 g.) was converted into the acid chloride by treatment with an excess of boiling thionyl chloride for 1.5 hours. The excess thionyl chloride was removed by distillation and the residual acid chloride was

treated carefully, with cooling and shaking, with freshly distilled 3 - aminopropylbenzene. The resulting dark mixture was immediately dissolved in aqueous ethanol, this solution was stirred with activated decolourizing charcoal for several hours, then filtered and concentrated. The resulting oily residue was dried in vacuo and then crystallised from an anhydrous mixture of ethanol and ether to furnish 11.5 g. of lustrous plates of the N - (3 - phenylpropyl)amide of 4(5) - imidazolyl - 2,2 - dimethylacetic acid as its hydrochloride. Recrystallisation from ethereal ethanol and then from pure ethanol afforded an analytically pure sample of the above amide hydrochloride which had m.p. 195—195.5°.

Lithium aluminium hydride (8 g.) was added in small portions to a well stirred warm suspension of the above amide hydrochloride (7.8 g.) in dry tetrahydrofuran. The mixture was heated under reflux for eight hours and then cooled and poured cautiously onto crushed ice. Sodium hydroxide (30 ml. of a 20% solution) was added and the organic layer was separated, dried and concentrated to yield 5 g. of an oil. The latter was treated with ethanolic hydrogen chloride and then with ether to yield crystals of 4(5) - [2 - (N - (3 - phenylpropyl)amino) - 1,1 - dimethylethyl]imidazole dihydrochloride (4 g.). Crystallisation from ethanol furnished the analytically pure material of m.p. 225—226°.

Example 37

N,N¹ - Bis[2 - (1 - benzylimidazol - 4 - yl)-ethyl]urea

A solution of sodium hydroxide (0.86 g.) in water (30 ml.) was added to 2 - benzyl - 5 - oxo - 5,6,7,8 - tetrahydro[1,5 - c]-pyrimidinium bromide (2.2 g.) and the mixture heated under reflux for 45 minutes. After cooling, the precipitated solid was filtered off and washed with water to give N,N¹ - bis - [2 - (benzylimidazol - 4 - yl)ethyl]urea (1.43 g.), m.p. 111—117°. An analytical sample, recrystallised from chloroform/cyclohexane, had m.p. 116—118°. The dipicrate (ex acetone/ether) had m.p. 157—159°.

Example 38

N,N¹ - Bis - [2 - (1 - benzylimidazol - 4 - yl)ethyl]urea

A mixture of N,N¹ - carbonyl diimidazole (0.24 g.) and 1 - benzyl - 4 - (2 - aminoethyl)imidazole base, prepared from the dihydrochloride (0.83 g.) by the method described in Example 23, was heated to 100° over 1 hour. After cooling, water was added to the reaction mixture to give N,N¹ - bis - [2 - (1 - benzylimidazol - 4 - yl)ethyl]urea (0.44 g.), m.p. 113—117°. Recrystallisation from chloroform/cyclohexane gave 0.32 g., m.p. 116—118°.

Example 39

1 - Benzyl - 4 - (2 - N - methoxycarbonyl-aminoethyl)imidazole picrate

A solution of 2 - benzyl - 5 - oxo - 5,6,7,8 - tetrahydromidazo[1,5 - c]pyrimidinium bromide (0.44 g.) in methanol (50 ml.) was heated under reflux for 4 hours. The solution was concentrated to low volume and a solution of excess picric acid in methanol was added. Addition of water gave 1 - benzyl - 4 - (2 - N - methoxycarbonylaminoethyl) - imidazole picrate (0.66 g.), m.p. 176—178°, undepressed on admixture with a sample prepared by reaction of 1 - benzyl - 4(2 - aminoethyl)-imidazole with methyl chloroformate.

Example 40

N,N¹ - Bis - [2 - (4 - imidazolyl)ethyl]urea

An intimate mixture of 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (1.37 g.) and histamine base (1.1 g.) was heated at 180° for five minutes. After cooling, the residue was dissolved in hot water and concentrated aqueous potassium carbonate solution added to give N,N¹ - bis - [2 - (4 - imidazolyl)ethyl]urea (1.84 g.), m.p. 187—189°.

Example 41

N - [2 - (4 - Imidazolyl)ethyl] - N¹ - amidinourea dihydrochloride

A solution of sodium ethoxide (prepared from 0.34 g. sodium) in ethanol (20 ml.) was added to a solution of guanidine hydrochloride (1.39 g.) in ethanol (20 ml.). After removal of sodium chloride 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (2 g.) was added and the mixture heated under reflux overnight. After evaporation to dryness the residue was dissolved in hot isopropyl alcohol and decolourised with charcoal. Addition of ethanolic hydrogen chloride followed by ether gave crude N - [2 - (4 - Imidazolyl)ethyl] - N¹ - amidinourea dihydrochloride m.p. 208—210°. Recrystallisation from methanol/ether gave a pure sample, m.p. 219.5—221.5°.

Example 42

1 - Methyl - 5 - oxo - 5,6,7,8 - tetrahydro-imidazo[1,5 - c]pyrimidine

A solution of sodium ethoxide (from 2.3 g. sodium) in ethanol (100 ml.) was added to a solution of 4 - methyl - 5 - (2 - aminoethyl)-imidazole dihydrochloride (9.9 g.) in ethanol (100 ml.) and the mixture heated under reflux for 2 hr. After cooling, the mixture was filtered and the filtrate evaporated to dryness. The resulting basic oil was reacted with N,N¹ - carbonyl di - imidazole (13 g.) by the method described in Example 1 to give 4.63 g. of the required product, m.p. 232—234°.

Example 43

1,5 - Dimethyl - 4 - (2 - aminoethyl)imidazole dihydrochloride

Reaction of 1 - methyl - 5 - oxo - 5,6,7,8 -

tetrahydroimidazo[1,5 - c]pyrimidine (2.3 g.) with methyl iodide (17 g.) in dimethylformamide (50 ml.) by the method described in Example 2 gave 1,2 - dimethyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]-pyrimidinium iodide (3.5 g.), m.p. 205—209°. An analytical sample, recrystallised from methanol/ether had m.p. 216—218°.

A solution of this quaternary salt (2.3 g.) in 1N sodium hydroxide solution (20 ml.) was heated under reflux overnight, cooled, and acidified with hydrochloric acid. This solution was evaporated to dryness and the residue purified by ion-exchange chromatography to give 1,5 - dimethyl - 4(2 - aminoethyl)-imidazole dihydrochloride (0.95 g.), m.p. 239—241°. Recrystallisation from methanol/ether gave 0.85 g., m.p. 240—242°.

Example 44

4 - Methyl - 5 - (2 - methylaminoethyl)-imidazole dihydrochloride

Finely powdered 1 - methyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (2 g.), was added portionwise to a stirred suspension of lithium aluminium hydride (1.8 g.) in tetrahydrofuran (125 ml.), and the mixture heated under reflux for 2 hours. After cooling, water was added, the mixture filtered and the inorganic products washed with hot methanol. The filtrate was acidified with ethanolic hydrogen chloride, the solution evaporated to dryness and the residual hydrochloride purified by ion-exchange chromatography to give 4 - methyl - 5 - (2 - methylaminoethyl)imidazole dihydrochloride (0.46 g.), m.p. 272—274°. An analytical sample, recrystallised from ethanol/methanol, had m.p. 275—277°.

Example 45

1 - (3 - Phenylpropyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine

4 - (3 - Phenylpropyl) - 5 - (2 - aminoethyl)imbidazole was precipitated from an aqueous solution of the hydrochloride (10.42 g.) by the addition of aqueous potassium carbonate solution. After decantation of the aqueous phase, the precipitated oil (which was insoluble in chloroform) was dissolved in ethanol and the solution filtered. The filtrate was evaporated to dryness under reduced pressure and the final traces of solvent removed by heating at 100°/0.1 mm. N,N^1 - Carbonyl di - imidazole (8.3 g.) was added rapidly to a solution of the base in dry dimethylformamide (200 ml.) and the mixture heated with stirring to 100° over 1 hour and at 100—110° for a further 30 minutes. After cooling, the solution was evaporated to dryness, water added to the residue, and the precipitated solid recrystallised from ethanol/cyclohexane to give 1 - (3 - phenylpropyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (5.41 g.), m.p. 142—145°. The mother liquors furnished a further 0.27 g., m.p. 143—145°, after filtration through silica gel and elution with 250 ml. of ethyl acetate/methanol (25 : 1). An analytical sample (ex ethanol) had m.p. 145—147°.

Example 46

1 - (n - Hexyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine

Reaction of 4 - n - hexyl - 5 - (2 - aminoethyl)imidazole (4.4 g.) with N,N^1 - carbonyl di - imidazole (6.8 g.) in dimethyl formamide by the method described in Example 45 gave 1 - (n - hexyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (2.2 g.), which was purified by filtration of an ethyl acetate solution through silica gel. An analytically pure sample (ex benzene - petroleum ether) had m.p. 114—115°.

Example 47

1 - Benzyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine

4 - Benzyl - 5 - (2 - aminoethyl)imidazole dihydrochloride (20 g.) was added to a saturated potassium carbonate solution and the mixture extracted seven times with chloroform. The extracts were dried ($MgSO_4$), evaporated to dryness and the residue reacted with N,N^1 - carbonyl di - imidazole (13.8 g.) in dimethylformamide as described in Example 45. After removal of the solvent, addition of water to the residue gave the required product (10.3 g.), m.p. 175—177°. Recrystallisation from isopropanol/cyclohexane gave 9.07 g., m.p. 178—180°.

Example 48

4 - (n - Hexyl) - 5 - [2 - N - (3 - phenylpropyl)aminoethyl]imidazole dihydrobromide

1 - (n - Hexyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (1.7 g.) was reacted with sodium hydride (0.46 g., 40%) and 3 - phenylpropyl bromide (1.53 g.) in dimethylformamide by the method described in Example 16. After removal of the solvent, the residue was dissolved in benzene, filtered from inorganic material, and washed with water. Benzene was evaporated under reduced pressure and the residue was dissolved in ethanol and acidified with hydrogen chloride. The addition of ether precipitated the hydrochloride of 1 - (n - hexyl) - 6 - (3 - phenylpropyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (2.4 g.).

This hydrochloride (2.2 g.) was hydrolysed with aqueous potassium hydroxide by the method described in Example 16. The base was isolated, dissolved in ethanol and acidified with gaseous hydrogen bromide. The addition of ether precipitated the product dihydrobromide which was obtained solid by the slow addition of its solution in anhydrous ethanol to a large excess of anhydrous ether. Repeating this process yielded 4 - (n - hexyl) - 5 -

[2 - N - (3 - phenylpropyl)aminoethyl]-imidazole dihydrobromide as a white solid (1.03 g.), m.p. 118—120°.

Example 49

4 - (3 - Phenylpropyl) - 5 - [2 - N - (3 - phenylpropyl)aminoethyl]imidazole dihydrochloride

1 - (3 - Phenylpropyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (5.54 g.) was reacted with sodium hydride (1.3 g., 40%) and 3 - phenylpropyl bromide (4.32 g.) in dimethylformamide (120 ml.) by the method described in Example 16. The reaction mixture was filtered, the filtrate evaporated to dryness, and the residue dissolved in a minimum of ethyl acetate. After filtration, the filtrate was passed rapidly through silica gel and eluted with 300 ml. of ethyl acetate/methanol (25.1). The oil obtained after evaporation was dissolved in ethanol, the solution acidified with ethanolic hydrogen chloride and ether added to precipitate the hydrochloride of 1,6 - di - (3 - phenylpropyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]-pyrimidine (7.7 g.) as a crude oil.

A portion of this hydrochloride (3.85 g.) was dissolved in ethanol (50 ml.) and hydrolysed with aqueous potassium hydroxide by the method described in Example 16. After acidification of the reaction mixture with hydrochloric acid the solution was evaporated to dryness, dry ethanol added, and the solution filtered. Further evaporation and addition of ethanol and then ether gave 4 - (3 - phenylpropyl) - 5 - [2 - N - (3 - phenylpropyl)-aminoethyl]imidazole dihydrochloride (2.6 g.), m.p. 161—163°.

Example 50

4 - (3 - Phenylpropyl) - 5 - (2 - N - n - hexylaminoethyl)imidazole dihydrochloride

1 - (3 - Phenylpropyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (2.2 g.) was reacted with sodium hydride (0.52 g.) and n - hexyl bromide (1.42 g.) in dimethylformamide (60 ml.) by the method described in Example 48. The hydrochloride of 1 - (3 - phenylpropyl) - 6 - hexyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine was obtained as a crude oil which was hydrolysed by the method described in Example 49, to give 4 - (3 - phenylpropyl) - 5 - (2 - N - n - hexylaminoethyl)imidazole dihydrochloride (1.14 g.), m.p. 168—170°.

Example 51

4 - Benzyl - 5 - [2 - N - (3 - phenylpropyl)-aminoethyl]imidazole dimaleate

1 - Benzyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c] - pyrimidine (4 g.) was reacted with sodium hydride (1.05 g., 40%) and phenylpropyl bromide (3.5 g.) in dimethylformamide (140 ml.) by the method described in Example 16. The hydrochloride of 1 - benzyl - 6(3 - phenylpropyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine was obtained as a crude oil by the method previously described in Example 48. This was then hydrolysed with potassium hydroxide, and the oily hydrochloride, obtained after addition of hydrochloric acid and evaporation to dryness, converted to the base by addition of aqueous potassium carbonate. Extraction with chloroform, drying ($MgSO_4$) and evaporation gave the crude base which was dissolved in methanol and added to a solution of maleic acid in methanol. Addition of ether gave the required dimaleate (7.17 g.), m.p. 133—135°, which, after recrystallisation from isopropanol, gave the pure product (6.45 g.), m.p. 137.5—138.5°.

Example 52

4 - Benzyl - 5 - (2 - n - hexylaminoethyl)-imidazole dimaleate

1 - Benzyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (4 g.) was reacted with sodium hydride (1.05 g. 40%) and n - hexyl bromide (2.91 g.) in dimethylformamide (150 ml.) by the method described in Example 16. The hydrochloride of the intermediate 1 - benzyl - 6 - hexyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]-pyrimidine was obtained as a crude oil by the method previously described in Example 48. This was converted to 4 - benzyl - 5 - (2 - n - hexylaminoethyl)imidazole dimaleate (5.77 g.), m.p. 120—121° by the method described in Example 51. Recrystallisation from isopropanol gave the pure product (5.48 g.), m.p. 122—123°.

Example 53

1,5 - Dibenzyl - 4 - (2 - aminoethyl)imidazole dihydrochloride

1 - Benzyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidine (1 g.) was reacted with benzyl bromide by the method described in Example 4, to give 1,2 - dibenzyl - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]pyrimidinium bromide (1.71 g.), m.p. 219—221°.

This quaternary salt was hydrolysed with 5N hydrochloric acid by the method described in Example 5, to give 1,5 - dibenzyl - 4 - (2 - aminoethyl)imidazole dihydrochloride (1.23 g.), m.p. 221—223°.

Recrystallisation gave the pure product (1.08 g.), m.p. 224—227°.

Example 54

1 - Pivaloyloxymethyl - 4 - (2 - phthalimidoethyl)imidazole

A solution of pivaloyloxymethyl chloride (5.7 g.) in dimethylformamide (120 ml.) was added dropwise over 30 minutes to a stirred mixture of potassium carbonate (4.98 g.) and 4 - (5) - (2 - phthalimidoethyl)imidazole (8.44 g.) in dimethylformamide (120 ml.),

while the temperature was maintained between 40—50°. After addition the temperature was raised to 90° and the mixture stirred at this temperature overnight. After cooling, the solution was filtered, evaporated to dryness and the residue dissolved in chloroform. After filtration, this solution was chromatographed on silica gel. Elution with ethyl acetate/methanol (10:1) separated the product from starting material to give 1 - pivaloyloxymethyl - 4(2 - phthalimidoethyl)imidazole (9.5 g.), m.p. 119—122°. An analytical sample, recrystallised from hexane/carbon tetrachloride, had m.p. 122—124°.

Example 55

1 - Benzyl - 5(2 - aminoethyl)imidazole dihydrochloride

A stirred solution of 1 - pivaloyloxymethyl - 4 - (2 - phthalimidoethyl)imidazole (2.7 g.) in benzyl bromide (25 ml.) was heated at 90° overnight. After removal of the unchanged benzyl bromide under reduced pressure the residual oil was dissolved in ethanol and poured into excess ether to precipitate 1 - pivaloyloxymethyl - 3 - benzyl - 4 - (2 - phthalimidoethyl)imidazolium bromide as a hygroscopic solid.

Ammonia gas was passed into a solution of this quaternary salt in methanol (60 ml.) until saturated at room temperature (ca. 30 minutes), and the mixture left to stand for a further 30 minutes. After evaporation to dryness, the residue was dissolved in chloroform, and after filtration, the solution chromatographed on silica gel. Elution with ethyl acetate/methanol (9:1), saturated with ammonia, gave, after evaporation and addition of isopropanolic hydrogen chloride, 1 - benzyl - 5 - (2 - phthalimidoethyl)imidazole hydrochloride (1.89 g.), m.p. 227—228°. Recrystallisation from isopropyl alcohol/ether gave 1.76 g., m.p. 230—232°.

This phthalimido derivative (2.1 g.) was hydrolyzed with 5N - hydrochloric acid by the method described in Example 15, to give 1 - benzyl - 5 - (2 - aminoethyl)imidazole dihydrochloride (1.075 g.), m.p. 222—223°, after recrystallisation from ethanol.

Example 56

1 - Methyl - 5(2 - aminoethyl)imidazole dihydrochloride

A stirred mixture of 1 - pivaloyloxymethyl - 4 - (2 - phthalimidoethyl)imidazole (5 g.), methyl iodide (16 g.) and dimethylformamide (25 ml.) was heated under reflux overnight. After evaporation to dryness the residue was dissolved in methanol and ether added to give 1 - pivaloyloxymethyl - 3 - methyl - 4 - (2 - phthalimidoethyl)imidazolium iodide (6.96 g.), m.p. 160—162°.

Hydrazine hydrate (4 ml.) was added to a solution of the above imidazolium salt (2.7 g.) in ethanol (150 ml.) and the mixture heated under reflux overnight. After cooling, the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. Palladised charcoal (0.5 g., 10%) and aqueous potassium carbonate solution were added, and the mixture stirred for 48 hours, and then filtered. The filtrate was evaporated to dryness, extracted with isopropyl alcohol and the cold extracts filtered.

Addition of ethanolic hydrogen chloride followed by ether gave the crude dihydrochloride of 1 - methyl - 5 - (2 - aminoethyl)-imidazole, which was purified by ion exchange chromatography (Zeo-Karb 225) to give the pure product, m.p. 268—269°.

Example 57

1 - Benzyl - 5,6,7,8 - tetrahydroimidazo[4,5 - c]pyridine dihydrochloride

1 - Pivaloyloxymethyl - 4 - (2 - phthalimidoethyl)imidazole (1.3 g.) was converted to 1 - pivaloyloxymethyl - 3 - benzyl - 4 - (2 - phthalimidoethyl)imidazolium bromide by the method described in Example 55. This quaternary salt was added to 5N hydrochloric acid (25 ml.) and the mixture heated under reflux overnight. After cooling, the solution was filtered and evaporated to dryness. The residue was basified with aqueous potassium carbonate solution and extracted with chloroform. After drying ($MgSO_4$), the chloroform was removed and ethanolic hydrogen chloride added to the residue to give 1 - benzyl - 5,6,7,8 - tetrahydroimidazo[4,5 - c]pyridine dihydrochloride as a hygroscopic crystalline solid. Recrystallisation twice from ethanol/ether gave an analytical sample, m.p. 192—194° (closed capillary).

Example 58

4 - t - Butyl - 5 - (2 - aminoethyl)imidazole dihydrochloride

Sulphuryl chloride (167 g.) was added dropwise to a solution of ethyl 4,4 - dimethyl - 3 - oxo - pentanoate (210 g.) in chloroform (150 ml.). The temperature of the reaction mixture was not allowed to rise above 35°. After addition, the mixture was stirred for 3 hours at room temperature and then heated under reflux until evolution of hydrogen chloride had ceased. The mixture was then washed with water, sodium bicarbonate solution and water. After drying ($MgSO_4$), the solvent was removed and the residue distilled to give ethyl 2 - chloro - 4,4 - dimethyl - 3 - oxo - pentanoate (213 g.), b.p. 112—117°/13 mm.

A mixture of ethyl 2 - chloro - 4,4 - dimethyl - 3 - oxo - pentanoate (170 g.), redistilled formamide (370 g.) and water (17 ml.) was heated at 150° for 5 hours. After cooling, the mixture was poured into water and the precipitated solid filtered off to give ethyl 4 - t - butylimidazole - 5 - carboxylate, m.p. 148—150°. A solution of this ester (40

g.) in tetrahydrofuran (375 ml.) was added to a stirred suspension of lithium aluminium hydride (9.3 g.) in tetrahydrofuran (150 ml.) and the mixture stirred for 3½ hours at room temperature. Sufficient water was added to decompose the complex, the mixture filtered and the inorganic solids washed with tetrahydrofuran and methanol. Evaporation and addition of acetone gave 4 - t - butyl - 5 - hydroxymethylimidazole (21 g.), m.p. 161—163°. An analytical sample (ex acetone) had m.p. 164—165°.

4 - t - Butyl - 5 - hydroxymethylimidazole (22 g.) was added portionwise to thionyl chloride (77 g.) and the mixture heated under reflux on a steam bath for 30 minutes. Removal of excess thionyl chloride and addition of ether gave 4 - t - butyl - 5 - chloromethylimidazole hydrochloride (29 g.) as a crude solid. A solution of this chloro compound (21 g.) in ethanol (250 ml.) was added dropwise to a suspension of sodium cyanide (49 g.) in water (80 ml.) held at 0°, and then stirred at 0° for a further hour. The mixture was filtered, the inorganic solids washed with ethanol and the filtrate evaporated to dryness. Recrystallisation from benzene gave 4 - t - butyl - 5 - cyanomethylimidazole, m.p. 103—108°. An analytical sample (ex benzene) had m.p. 109—109.5°.

A solution of 4 - t - butyl - 5 - cyanomethylimidazole (6.5 g.) in ethanol (300 ml.), saturated with ammonia at —10°, was hydrogenated over Raney nickel catalyst at 150 atmospheres/150° for 3 hours. After cooling the solution was concentrated, acidified with ethanolic hydrogen chloride, and ether added to give 4 - t - butyl - 5 - (2 - aminoethyl)-imidazole dihydrochloride (7.6 g.), m.p. 289—293°.

Example 59

4 - Isopropyl - 5 - (2 - aminoethyl)imidazole dihydrochloride

A solution of sodium nitrite (43.8 g.) in water (92 ml.) was added dropwise, with stirring, to a solution of ethyl isobutyrylacetate (100.3 g.) in acetic acid (80 ml.) at 0°. After stirring at 0° for 30 minutes then at room temperature for 3 hours, water (100 ml.) was added and the mixture extracted with ether. The extracts were washed with water, saturated sodium bicarbonate solution and water. After drying ($CaSO_4$), the solution was evaporated to give ethyl 2 - oximino - 4 - methyl - 3 - oxopentanoate (112 g.) as a crude oil.

A solution of this oximinoketone (219 g.) in ethanol (280 ml.) was added to a suspension of pre-reduced palladised charcoal (10 g., 10%) in ethanol (1 l.) and saturated ethanolic hydrogen chloride (512 ml.) and the mixture hydrogenated at room temperature and pressure until the theoretical amount of hydrogen was taken up. The mixture was filtered, the filtrate concentrated and ethyl acetate added to give ethyl 2 - amino - 4 - methyl - 3 - oxo - pentanoate hydrochloride (230.6 g.), m.p. 129—131° (dec.).

This aminoketone (50.5 g.) was dissolved in redistilled formamide (180 ml.) and the solution heated at 120° for 2 hours, 130° for 1 hour, and finally at 140° for 2 hours. After cooling, the mixture was filtered and the crystalline product washed with water to give ethyl 4 - isopropylimidazole - 5 - carboxylate (22 g.), m.p. 177—178°.

This ester (108 g.) was placed in a soxhlet and reduced with lithium aluminium hydride (34.5 g.) in tetrahydrofuran by the method described in Example 58 to give 4 - hydroxymethyl - 5 - isopropylimidazole (62.3 g.), m.p. 121—123°.

This alcohol (74 g.) was converted to 4 - chloromethyl - 5 - isopropylimidazole hydrochloride (96.6 g.), m.p. 185—189° by the method described in Example 58.

Reaction of this chloro compound (39 g.) with sodium cyanide (98 g.) by the method described in Example 58 gave 4 - cyanomethyl - 5 - isopropylimidazole (10.1 g.), m.p. 153—154° after recrystallisation of the crude product from water.

Catalytic reduction of this nitrile (8.1 g.) by the method described in Example 58 gave 4 - isopropyl - 5 - (2 - aminoethylimidazole dihydrochloride (9 g.), m.p. 206—208°, after recrystallisation of the crude product from ethanol - ether.

Example 60

4 - (3 - Phenylpropyl) - 5 - (2 - aminoethyl)-imidazole dihydrochloride

A solution of 5 - phenylpent - 1 - yne (320 g.) in tetrahydrofuran (500 ml.) was added dropwise with stirring over 30 min. to a suspension of lithamide (90 g.) in liquid ammonia (2½ lit.). After addition, the mixture was allowed to boil under reflux for 8 hours, cooled to —65° overnight and then ethylene oxide (288 g.) added in one portion. The mixture was stirred for a further 2 days, ammonium chloride (211 g.) added cautiously and the ammonia allowed to evaporate. Water (500 ml.) was added to the solid residue, the organic layer extracted with ether, and the combined extracts dried ($MgSO_4$). After removal of ether the residue was distilled to give 7 - phenylhept - 3 - yn - 1 - ol (355 g.), b.p. 104—106°/0.03 mm.

7 - Phenylhept - 3 - yn - 1 - ol (355 g.) was added during 45 min. to a stirred slurry of toluene - p - sulphonyl chloride (399 g.) in pyridine (400 ml.) maintained at 20±2°. After stirring for a further 2 hr. at room temperature the mixture was poured onto crushed ice and extracted with ether. The ethereal solution was washed with 6N sulphuric acid (2×200 ml.) and then successively with water (2×300 ml.), saturated sodium

bicarbonate solution (2×200 ml.) and water (200 ml.). After drying ($MgSO_4$), the ether was removed to give 7 - phenylhept - 3 - ynyl toluene - p - sulphonate (615 g.) as a crude oil, which was used without further purification.

A stirred mixture of 7 - phenylhept - 3 - ynyl toluene - p - sulphonate (608 g.) and potassium phthalimide (340 g.) in dimethylformamide (3.5 lit.) was heated on a steam bath for 2 hr. The mixture was then concentrated under reduced pressure and poured into water (2 lit.). The precipitated solid was collected and recrystallised from ethanol/water to give 1 - phthalimido - 7 - phenylhept - 3 - yne (350 g.), m.p. 69—71°. An analytical sample had m.p. 72—73°.

A solution of hydrated magnesium sulphate (62 g.) in water (400 ml.) was added to a solution of 1 - phthalimido - 7 - phenylhept - 3 - yne (31 g.) in 'Analar' acetone (2 lit.). To this stirred, cooled mixture was added rapidly a solution of potassium permangate (27.8 g.) in water (1600 ml.). The temperature was not allowed to rise above 25°C, after which the mixture was stirred for 6 hr. at room temperature. The colour due to permanganate, which was barely perceptible was then discharged with a few drops of aqueous sodium bisulphite solution, and the mixture filtered. The inorganic residue and the filtrate were extracted thoroughly with chloroform and the combined extracts dried ($MgSO_4$). Removal of the solvent gave a yellow oil which crystallised on addition of ethanol/water to give 1 - phthalimido - 7 - phenylheptane - 3,4 - dione (24 g.), m.p. 80—82°.

Paraformaldehyde (7.2 g.) was added in one portion to a solution of 1 - phthalimido - 7 - phenylheptane - 3,4 - dione (27 g.) and ammonium acetate (48 g. recrystallised from dry ethanol/ether) in dry acetic acid (600 ml.) maintained at 50°C. The mixture was stirred at 50° for 3 hr., cooled and poured into an equal volume of water. This solution was then neutralised with a solution of potassium carbonate and during this procedure the solution was extracted with chloroform at three separate pH's (i.e. pH 5, pH 7, and pH 10). Evaporation of the middle extract (pH 7) and addition of ethanolic hydrogen chloride followed by ethyl acetate gave 4 - (3 - phenylpropyl) - 5 - (2 - phthalimidoethyl)imidazole hydrochloride (9.9 g.), m.p. 201.5—202.5°. The mother liquors were evaporated to dryness, basified with potassium carbonate solution and extracted with chloroform and these extracts combined with the previous extracts at pH 5 and pH 10. Removal of chloroform and chromatography of the residue on silica gel, eluting first with ethyl acetate to remove impurities followed by ethyl acetate/ethanol, (25:2 and then 25:3) gave a further 3.64 g. of the required hydrochloride salt, m.p. 201.5—203°, after acidification with ethanolic hydrogen chloride.

A solution of 4 - (3 - phenylpropyl) - 5 - (2 - phthalimidoethyl)imidazole hydrochloride (2.0 g.) in 5N hydrochloric acid (50 ml.) and acetic acid (4 ml.) was heated under reflux for 12 hr. After cooling to 0° the reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure. Addition of ethanol and further evaporation to dryness gave a solid residue, which was recrystallised from dry ethanol/tetrahydrofuran to give 4 - 3 - (phenylpropyl) - 5 - (2 - aminoethyl)-imidazole dihydrochloride (1.49 g.); m.p. 161—163°. Recrystallisation from ethanol/ether gave an analytical sample, m.p. 163—164°.

Example 61

4 - Ethyl - 5 - (2 - aminoethyl)imidazole dihydrochloride

Reaction of hex - 3 - yn - 1 - ol (49 g.) with toluene - p - sulphonyl chloride (108 g.) in pyridine (50 ml.), by the method described in Example 60, gave hex - 3 - ynyl toluene - p - sulphonate (123 g.) as a crude oil, which was used without further purification.

Hex - 3 - ynyl toluene - sulphonate (63 g.) and potassium phthalimide (47 g.) were reacted together by the method described in Example 60. The crude product was dissolved in a minimum of hot benzene and, after cooling, the solution was filtered to remove unreacted phthalimide. The filtrate was evaporated to dryness and the residue recrystallised from aqueous ethanol to give 1 - phthalimidohex - 3 - yne (33 g.), m.p. 81—83°. An analytical sample had m.p. 84—85°.

Oxidation of 1 - phthalimidohex - 3 - yne (17.2 g.) with buffered potassium permanganate, by the method described in Example 60 gave 1 - phthalimido - 3,4 - hexanedione (14.1 g.), m.p. 87—89°. An analytical sample (ex ethanol/water) had m.p. 89—91°.

Reaction of 1 - phthalimido - 3,4 - hexanedione (10.2 g.) with paraformaldehyde and ammonium acetate by the method described in Example 60 gave a crude base which was purified by chromatography on neutral alumina. Elution with ethanol/ethyl acetate (1:19, 1:9 and then 1:1) gave 4 - ethyl - 5 - (2 - phthalimidoethyl)imidazole hydrochloride (1.46 g.), m.p. 244—247°, after evaporation and addition of isopropanolic hydrogen chloride and ethyl acetate.

Hydrolysis of 4 - ethyl - 5 - (2 - phthalimidoethyl)imidazole hydrochloride (1.23 g.) with 5N hydrochloric acid by the method described in Example 15 gave 4 - ethyl - 5 - (2 - aminoethyl)imidazole dihydrochloride (0.73 g.), m.p. 168.5—170.5°. An analytical sample, recrystallised from ethanol/ether, had m.p. 170—171°.

Example 62

4 - (Hexyl) - 5 - (2 - aminoethyl)imidazole

Reaction of 1 - octyne (244 g.) with ethylene oxide (288 g.) and lithamide (61 g.) in liquid ammonia (1.2 l.) by the method described in Example 60 gave dec - 3 - yne - 1 - ol (111 g.), b.p. 148°/50 mm. Reaction of dec - 3 - yn - 1 - ol (116 g.) with toluene - p - sulphonyl chloride (143 g.), by the method described in Example 60 gave dec - 3 - ynyl toluene - p - sulphonate (210 g.) as a crude oil, which was used without further purification.

A mixture of dec - 3 - ynyl toluene - p - sulphonate (150 g.), phthalimide (64 g.) and potassium carbonate (30 g.) in dimethyl sulphoxide (1 l.) was heated for 74 hours at 60°. Additional potassium carbonate 3 g.) and phthalimide (6.5 g.) were added and heating was continued at 80° for 24 hours. After adding to water and extracting with benzene, 1 - phthalimidodec - 3 - yne (82 g.) was isolated from the benzene concentrate as a low-melting solid and purified by recrystallising from acetone in the cold.

Oxidation of 1 - phthalimidodec - 3 - yne (32 g.) with buffered potassium permanganate, by the method described in Example 60 gave 1 - phthalimido - 3,4 - decanedione (31 g.), m.p. 69—71°. An analytical sample (ex ethanol/water) had m.p. 74—75°.

Reaction of 1 - phthalimido - 3,4 - decanedione (50 g.) with paraformaldehyde and ammonium acetate, by the method described in Example 60 gave a crude base which was purified by chromatography on silica gel SG32 and neutral alumina. Chromatographically pure samples of the base were acidified with hydrogen chloride affording 4 - n - hexyl - 5 - (2 - phthalimidoethyl)imidazole hydrochloride m.p. 152—154°. An analytically pure sample (ex ethanol/ethyl acetate/ether) had m.p. 159—161°.

Hydrolysis of 4 - n - hexyl - 5 - (2 - phthalimidoethyl)imidazole hydrochloride (6.0 g.) with 5N hydrochloric acid by the method described in Example 60 gave 4 - n - hexyl - 5 - (2 - aminoethyl)imidazole hydrochloride as an oil. The base was obtained by the addition of aqueous potassium carbonate followed by chloroform extraction. The residue from the chloroform extracts was dissolved in methanol and filtered through silica gel. Concentration of the methanol gave a chromatographically pure sample of 4 - n - hexyl - 5 - (2 - aminoethyl)imidazole as a light coloured oil which was used directly for the preparation of 1 - (n - hexyl) - 5 - oxo - 5,6,7,8 - tetrahydroimidazo[1,5 - c]-pyrimidine.

Example 63

4 - Benzyl - 5 - (2 - aminoethyl)imidazole dihydrobromide

A solution of 4 - phenyl - 4,5,6,7 - tetrahydroimidazo[4,5 - c]pyridine (30 g.) in glacial acetic acid (600 ml.) was hydrogenated over palladium on charcoal (10%) at 100 atmospheres for 26 hr. After removal of the catalyst and evaporation to dryness, the residue was dissolved in nitromethane and the solution acidified with hydrogen bromide gas. Addition of ether precipitated the crude product which was recrystallised from 2 - ethoxyethanol/nitromethane to give 4 - benzyl - 5 - (2 - aminoethyl)imidazole dihydrobromide (43.2 g.), m.p. 146—148°.

Example 64

4 - Phenyl - 5 - (2 - aminoethyl)imidazole dihydrochloride

4 - Chlorobutyrophenone (366 g.) was added slowly to a solution of phthalimide (294 g.) and potassium carbonate (138 g.) in dimethylformamide (1500 ml.) at 98°. Heating was continued at this temperature for 18 hours and the mixture was then added to water. Precipitated solid was collected and treated with hot benzene. The benzene extracts were allowed to cool and the solid which crystallised was removed by filtration. Concentration of the filtrate followed by recrystallisation from ethanol yielded 4 - phthalimidobutyrophenone, m.p. 132—133°.

4 - Phthalimidobutyrophenone (58.6 g.) was dissolved in benzene (200 ml.) and a solution of bromine (32 g.) in benzene (20 ml.) was added dropwise over 15 minutes. The solvent was then removed under reduced pressure and the residue was recrystallised from ethanol, yielding 2 - bromo - 4 - phthalimidobutyrophenone (69.1 g.). Analytically pure material, m.p. 122—124° was obtained by further recrystallisation from ethanol.

A mixture of 2 - bromo - 4 - phthalimidobutyrophenone (24 g.) formamide (80 ml.) and water (6.4 ml.) was heated under reflux for 10 hours at 170°. After cooling, concentrated hydrochloric acid (50 ml.) was added, which precipitated a solid (phthalimide 5.4 g.) which was subsequently removed by filtration. The filtrate was boiled under reflux for 1 hour and then cooled, filtered and concentrated. After filtration the filtrate was basified with ammonia and extracted with chloroform. Concentration of the chloroform extracts, followed by acidification of an ethanol solution of the residue with a solution of hydrogen chloride in isopropyl alcohol and the addition of ether afforded a white solid (7.3 g.). This was recrystallised from methanol - ethyl acetate yielding 4 - phenyl - 5 - (2 - aminoethyl)-imidazole dihydrochloride (5.5 g.), m.p. 262—264°.

Example 65

4 - Cyclohexyl - 5 - (2 - aminoethyl)imidazole dihydrochloride

4 - Phenyl - 5 - (2 - aminoethyl)imidazole dihydrochloride (0.5 g.) dissolved in a mixture of acetic acid (10 ml.) and 5N hydrochloric

acid (5 ml.) was added to a suspension of platinum oxide in 5N hydrochloric acid, which had been previously reduced with hydrogen. Hydrogenation was carried out at atmospheric pressure with moderate heating (60°). After the absorption of hydrogen was complete, the catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallised from ethanol - ethyl acetate affording 4 - cyclohexyl - 5 - (2 - aminoethyl)imidazole dihydrochloride (0.37 g.), m.p. 244—247°.

Example 66

4 - (p - Tolyl) - 5 - (2 - aminoethyl)imidazole dihydrochloride

4 - Chloro - 4′ - methyl butyrophenone (197 g.) was reacted with phthalimide (147 g.) and potassium carbonate (69 g.) according to the method described in Example 64. Recrystallisation from ethanol afforded 4 - phthalimido - 4′ - methylbutyrophenone m.p. 118—119°.

Bromination of this ketone (30.8 g.) as described in Example 64 yielded 2 - bromo - 4 - phthalimido - 4′ - methylbutyrophenone (35 g.), m.p. 132—134° (from ethanol). A mixture of the bromoketone (30 g.) and formamide (100 ml.) was heated at 180—195° for 4 hours. After cooling, dilute hydrochloric acid was added precipitating a solid which was removed by filtration. The filtrate was basified with aqueous ammonia precipitating a solid which was separated, dissolved in ethanol and acidified with a solution of hydrogen chloride in isopropyl alcohol. The addition of ether precipitated a solid which was collected and recrystallised from ethanol - ether - ethyl acetate, yielding 4 - (p - tolyl) - 5 - (2 - phthalimidoethyl)imidazole hydrochloride, m.p. 301—303°. Additional material, m.p. 295—300° was isolated from the aqueous reaction mixture.

The phthalimo derivative (2.4 g.) was hydrolysed with 5N hydrochloric acid (50 ml.) at reflux temperature for 24 hours. After cooling, phthalic acid was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. Recrystallisation of the residue three times from methanol - ether yielded 4 - (p - tolyl) - 5 - (2 - aminoethyl)-imidazole dihydrochloride (1.35 g.), m.p. 310—315°.

Example 67

4 - Phenyl - 5 - (2 - dimethylaminoethyl)-imidazole dihydrochloride

4 - Phenyl - 5 - (2 - aminoethyl)imidazole was obtained as an oil from its dihydrochloride (2.0 g.), sodium (0.32 g.) and ethanol. To the base was added formic acid (1.68 g.) and 40% formaldehyde (1.2 ml.) and the mixture was heated under reflux for 24 hours. Evaporation gave an oil which was dissolved in ethanol and treated with a solution of hydrogen chloride in isopropyl alcohol. The hydrochloride obtained was purified by ion-exchange chromatography to yield 4 - phenyl - 5 - (2 - dimethylaminoethyl)imidazole dihydrochloride monohydrate (0.58 g.), m.p. 220—222°.

Example 68

2 - Phenyl - 4(5) - (2 - aminoethyl)imidazole dihydrochloride

Sodium hydrogen carbonate (3.8 g.) was added in one portion to a stirred solution of 1 - bromo - 4 - phthalimidobutan - 2 - one (11.8 g.) and benzamidine hydrochloride (7 g.) in dimethylformamide (90 ml.) at room temperature. The reaction mixture was then warmed to 60° and a further quantity of sodium hydrogen carbonate (2.95 g.) added portionwise over 1 hour. After addition, the temperature was raised to 90° and stirring continued for a further 2 hours. The cold reaction mixture was filtered, the filtrate concentrated under reduced pressure and the resulting brown oil dissolved in chloroform.

After washing with water and drying ($MgSO_4$), the chloroform solution was concentrated and the residue acidified with ethanolic hydrogen chloride. Addition of ethyl acetate to the cloud point precipitated 2 - phenyl - 4(5) - (2 - phthalimidoethyl)imidazole hydrochloride (7.1 g.), m.p. 258—261°. A second crop (0.84 g.), m.p. 267—269°, was obtained on addition of more ethyl acetate. Recrystallisation from methanol afforded an analytical sample, m.p. 270—272°.

A solution of 2 - phenyl - 4(5) - (2 - phthalimidoethyl)imidazole hydrochloride (4.3 g.) in 5N hydrochloric acid (100 ml.) was heated under reflux overnight. After cooling to 0°, the mixture was filtered and the filtrate evaporated to dryness. The residue was recrystallised from methanol/ether to give 2 - phenyl - 4(5) - (2 - aminoethyl)imidazole dihydrochloride (2.5 g.), m.p. 305—306° (dec.).

Example 69

2 - p - Tolyl - 4(5) - (2 - aminoethyl)imidazole dihydrochloride

Reaction of p - toluamidine hydrochloride (3.4 g.) with 1 - bromo - 4 - phthalimidobutan - 2 - one (5.9 g.) by the method described in Example 68 gave 2 - p - tolyl - 4(5) - (2 - phthalimidoethyl)imidazole hydrochloride, m.p. 278—281° (dec.), after recrystallisation from methanol.

Acid hydrolysis of this phthalimido derivative by the method described in Example 68 gave 2 - p - tolyl - 4(5) - (2 - aminoethyl)-imidazole dihydrochloride, m.p. 290.5—292°, after recrystallisation from ethanol/ether.

Example 70

2 - (p - Chlorophenyl) - 4(5) - (2 - aminoethyl)imidazole dihydrochloride

Reaction of p - chlorobenzamidine hydrochloride (9.1 g.) with 1 - bromo - 4 -

phthalimidobutan - 2 - one (11.8 g.) by the method described in Example 68 gave crude 2 - (p - chlorophenyl) - 4(5) - (2 - phthalimidoethyl)imidazole hydrochloride (12 g.) which on recrystallisation from methanol/ether, gave pure material, m.p. 310—312° (dec.).

Acid hydrolysis of this phthalimido derivative by the method described in Example 68 gave 2 - (p - chlorophenyl) - 4(5) - (2 - aminoethyl)imidazole dihydrochloride, m.p. 301—303°, after recrystallisation from methanol/ether.

Example 71

2 - (p - Methoxyphenyl) - 4(5) - (2 - aminoethyl)imidazole dihydrochloride

Reaction of p - anisamidine hydrochloride (11.2 g.) with 1 - bromo - 4 - phthalimidobutan - 2 - one (17.7 g.) by the method described in Example 68 gave 2 - (p - methoxyphenyl) - 4(5) - (2 - phthalimidoethyl)-imidazole hydrochloride, m.p. 261—263°, after recrystallisation from methanol/ethyl acetate.

Acid hydrolysis of this phthalimido derivative (4.6 g.) with 5N hydrochloric acid by the method described in Example 68 gave 2 - (p - methoxyphenyl) - 4(5) - (2 - aminoethyl)imidazole dihydrochloride (3.2 g.), m.p. 246—250°. Recrystallisation from methanol/ether afforded an analytical sample, m.p. 256—257°.

Example 72

2 - Benzyl - 4(5) - (2 - aminoethyl)imidazole dihydrochloride

A solution of sodium ethoxide, prepared from sodium (2.6 g.), in anhydrous ethanol (60 ml.) was added dropwise, with stirring, to a solution of phenyl acetamidine hydrochloride (20.4 g.) in anhydrous ethanol (60 ml.). After addition the mixture was heated to reflux temperature and a hot solution of 1 - bromo - 4 - phthalimidobutan - 2 - one (11.8 g.) in ethanol (350 ml.) added dropwise, with stirring, over 3 hours. The mixture was heated under reflux for a further 2 hours, cooled, filtered and the filtrate evaporated to low volume. The residue was acidified with isopropanolic hydrogen chloride, ethyl acetate added to the cloud point, whereupon 2 - benzyl - 4(5) - (2 - phthalimidoethyl)imidazole hydrochloride (7.3 g.), m.p. 231—234°, crystallised out on standing. An analytical sample, recrystallised from ethanol, had m.p. 238—241°.

Acid hydrolysis of this phthalimido derivative (7 g.) with 5N hydrochloric acid by the method described in Example 68 gave 2 - benzyl - 4(5) - (2 - aminoethyl)imidazole dihydrochloride (3.5 g.), m.p. 238—240°. Recrystallisation from ethanol/ether followed by drying at 120°/0.1 mm., afforded an analytical sample, m.p. 253—256° (dec.).

Example 73

2 - o - Tolyl - 4(5) - (2 - aminoethyl)-imidazole dihydrochloride

A suspension of sodamide (10.5 g.) in benzene (100 ml.) was added rapidly to a stirred solution of o - tolunitrile (25 g.) in benzene (200 ml.) and the mixture stirred and heated under reflux for 5 hours. The excess sodamide was decomposed with water and, after separating, the benzene layer was washed with water and dried (Na_2SO_4). After removal of the benzene, the residue was acidified with isopropanolic hydrogen chloride to give o - toluamidine hydrochloride (24 g.), m.p. 238—241°, after recrystallisation from isopropanol/ether. An analytical sample had m.p. 243—246°.

Reaction of o - toluamidine hydrochloride (9.2 g.) with 1 - bromo - 4 - phthalimidobutan - 2 - one (5.2 g.) by the method described in Example 68 gave 2 - o - tolyl - 4(5) - (2 - phthalimidoethyl)imidazole hydrochloride, m.p. 244—247° (dec.), after recrystallisation from ethanol/ethyl acetate.

Acid hydrolysis of this phthalimido derivative (1.2 g.) with 5N hydrochloric acid (60 ml.) by the method described in Example 68 gave 2 - o - tolyl - 4(5) - (2 - aminoethyl)-imidazole dihydrochloride hydrate (0.67 g.), m.p. 207—210°. An analytical sample of the dipicrate had m.p. 20—201°.

Example 74

2 - (3 - Phenylpropyl) - 4(5) - (2 - aminoethyl)imidazole dihydrochloride

Reaction of 4 - phenylbutyramidine hydrochloride (23.8 g.) with 1 - bromo - 4 - phthalimidobutan - 2 - one (11.8 g.) by the method described in Example 68 gave 2 - (3 - phenylpropyl) - 4(5) - (2 - phthalimidoethyl)-imidazole hydrochloride, m.p. 186—189°, after recrystallisation from ethanol/ether.

Acid hydrolysis of this phthalimido derivative (2.2 g.) with 5N hydrochloric acid by the method described in Example 68 gave 2 - (3 - phenylpropyl) - 4(5) - (2 - aminoethyl)imidazole dihydrochloride (1.2 g.), m.p. 206—207°, after recrystallisation of the crude product from ethanol/ether.

Example 75

2 - Methyl - 4(5) - (2 - aminoethyl)imidazole dihydrochloride

A solution of sodium ethoxide, prepared from sodium (13.8 g.), in anhydrous ethanol (1200 ml.) was added dropwise, with stirring, to a solution of acetamidine hydrochloride (56.8 g.) in anhydrous ethanol (400 ml.). After addition, the mixture was heated to reflux temperature and a hot solution of 1 - bromo - 4 - phthalimidobutan - 2 - one (59.2 g.) in a mixture of ethanol (1 litre) and dimethylformamide (200 ml.) was added dropwise, with stirring, over 3 hours. The mixture was heated under reflux for a further 2 hours,

cooled, filtered and the filtrate evaporated to dryness. The residue was dissolved in ethanol, charcoaled and the filtrate acidified with ethanolic hydrogen chloride. Addition of ethyl acetate gave crude 2 - methyl - 4(5) - (2 - phthalimidoethyl)imidazole hydrochloride which was purified by precipitating the base from water with aqueous potassium carbonate solution. Reacidification of a solution of this base in ethanol with ethanolic hydrogen chloride gave the pure hydrochloride, m.p. 292—295° (dec.).

Acid hydrolysis of this phthalimido derivative (8.3 g.) with 5N hydrochloric acid by the method described in Example 68 gave 2 - methyl - 4(5) - (2 - aminoethyl)imidazole dihydrochloride (5.4 g.), m.p. 221—224°. An analytical sample, recrystallised from ethanol - ether had m.p. 222—224°.

Example 76

2,4 - Diphenyl - 5 - (2 - aminoethyl)imidazole dihydrochloride

(i) Sodium bicarbonate (3.8 g.) was added to a solution of 2 - bromo - 4 - phthalimidobutyrophenone (Example 64, 14.8 g.) and benzamidine hydrochloride hydrate (7.0 g.) in the minimum volume of dimethylformamide. The suspension was heated to 60° and more sodium bicarbonate (3.0 g.) was added over 0.5 hours. After addition the mixture was heated at 100° for 2 hours. Following concentration under reduced pressure water was added to the residue and the aqueous solution extracted with chloroform. The chloroform extracts were dried over calcium chloride and concentrated to dryness. The residue was dissolved in methanol, acidified with a solution of hydrogen chloride in isopropyl alcohol and diluted with ether. The white solid obtained was recrystallised from methanol - hydrogen chloride - ether to afford 2,4 - diphenyl - 5 - (2 - phthalimidoethyl)imidazole hydrochloride (8.7 g.), m.p. 161—162°.

(ii) A solution of 2,4 - diphenyl - 5 - (2 - phthalimidoethyl)imidazole hydrochloride (2.15 g.) and hydrazine hydrate (0.75 g.) in ethanol (30 ml.) was heated under reflux for 2 hours. After cooling, phthalhydrazide was removed by filtration and the residue was concentrated to dryness under reduced pressure. The residue was dissolved in ethanol, acidified with a solution of hydrogen chloride in isopropyl alcohol and diluted with ether. Recrystallisation from methanol - ether afforded 2,4 - diphenyl - 5 - (2 - aminoethyl)imidazole dihydrochloride (0.5 g.), m.p. 323—325°.

Example 77

2 - (p - Chlorophenyl) - 4 - phenyl - 5 - (2 - dimethylaminoethyl)imidazole dihydrobromide

(i) The reaction of 2 - bromo - 4 - phthalimidobutyrophenone (Example 64, 14.8 g.) and p - chlorobenzamidine hydrochloride (7.64 g.), under conditions similar to those described in Example 76, afforded 2 - (p - chlorophenyl) - 4 - phenyl - 5 - (2 - phthalimidoethyl)imidazole hydrochloride (11.5 g.), m.p. 238—240°.

(ii) Hydrolysis of the phthalimido derivative (10.3 g.) in concentrated hydrochloric acid (400 ml.) and glacial acetic acid (400 ml.) for 48 hours at reflux temperature afforded 2 - (p - chlorophenyl) - 4 - phenyl - 5 - (2 - aminoethyl)imidazole dihydrochloride (6.0 g., m.p. 322—3).

(iii) 2 - (p - chlorophenyl) - 4 - phenyl - 5 - (2 - aminoethyl)imidazole dihydrochloride (3.0 g.) was converted to the base and caused to react with formaldehyde (40%, 1.35 ml.) and formic acid (1.84 g.) according to the method described in Example 67. The product obtained was converted to the hydrobromide using hydrogen bromide in acetic acid and recrystallised from ethanol - ether to afford 2 - (p - chlorophenyl) - 4 - phenyl - 5 - (2 - dimethylaminoethyl)imidazole dihydrobromide (2.0 g.), m.p. 175—7°.

Example 78

2 - (4(5) - Imidazolylethyl)aminopropionitrile dihydrochloride

Acrylonitrile (5.3 g.) was added dropwise during 5 minutes to histamine (11.1 g.) in methanol at 25°. The mixture was stirred for 4 hours, then heated under reflux for 1.5 hours and finally, concentrated. The resulting oily residue was taken up in ethanol and acidified with hydrogen chloride to pH 3. 2 - (4(5) - Imidazolylethyl)aminopropionitrile dihydrochloride, which crystallised out, was collected and recrystallised from ethanol to afford prisms, m.p. 135—136°.

Example 79

4(5) - (3 - Isopropylaminopropyl)imidazole dihydrochloride

A mixture of 4(5) - (3 - aminopropyl)-imidazole (2.0 g.), acetone (1.1 g.) and ethanol (50 ml.) was hydrogenated at 40°C and 40 p.s.i. in the presence of platinum oxide catalyst. Following completion of hydrogen uptake, the catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was converted to the dipicrate (6.0 g.), m.p. 154—155° and ultimately to the required dihydrochloride, m.p. 154—157°.

Example 80

Bis - (4(5) - imidazolylmethyl)amine trihydrochloride

Finely powdered 4(5) - chloromethylimidazole hydrochloride (20 g.) was added portionwise during 10 minutes to liquid ammonia (200 ml.). The mixture was maintained at —20° for 8 hours after which time the ammonia was allowed to boil off. The residue was treated with aqueous potassium

carbonate, the mixture concentrated and the resulting solid extracted twice with cold (0°) isopropanol. Evaporation of the extract furnished a colourless oil which was converted into a colourless insoluble solid hydrochloride salt in anhydrous ethanol. The hydrochloride was washed with hot ethanol (500 ml.) and then crystallised twice from aqueous ethanol (1:10) to afford bis - (4(5) - imidazolylmethyl)amine trihydrochloride as colourless prisms, m.p. 246—8°. The m.p. was depressed by 25° on admixture with an authentic sample of the known 4(5) - imidazolylmethylamine dihydrochloride (which had m.p. 246—247°).

Example 81

N,N - Bis - (4(5) - imidazolylmethyl)aminoethanol trihydrochloride

2 - Aminoethanol (6.1 g.) was treated with sodium hydride (4.8 g. of 50% dispersion in paraffin oil) in dry toluene (50 ml.) at 50—60° for 2.5 hours until hydrogen evolution had ceased. The supernatant toluene layer was removed by decantation and replaced by dry dimethylsulphoxide (75 ml.). The mixture was stirred and to this was added dropwise 4(5) - chloromethylimidazole hydrochloride (7.6 g.) in dimethylsulphoxide (50 ml.) during 30 minutes. The mixture was maintained at 45—50° for a further 1 hour, then filtered and concentrated. The oily concentrate was added to 1 litre of hot saturated aqueous picric acid. The product which crystallised was collected and recrystallised twice from hot water to furnish N,N - bis - (4(5) - imidazolylmethyl)-aminoethanol tripicrate, as orange plates, m.p. 193—195°, (15 g.).

(From the mother liquors, there was also obtained 4(5) - (N - (2 - hydroxyethyl)aminomethyl)imidazole dipicrate, m.p. 212—214° (4 g.), (Example 32)). Conversion of the tripicrate into the trihydrochloride in the normal manner furnished crystals (from alcohol) m.p. 203—205°.

Example 82

Bis - (2 - (4(5) - Imidazolyl)ethyl)amine tripicrate

A mixture of histamine (3.12 g.), 4(5) - cyanomethylimidazole (3.0 g.) and methanol (25 ml.) was hydrogenated at 130° at a pressure of 100—110 atmospheres in the presence of Raney nickel (3 g.) for 3 hours. Following filtration and concentration, the crude product was converted into a picrate. Recrystallisation from water afforded bis - (2 - (4(5) - imidazolyl)ethyl-amine tripicrate in two crops: (3.43 g., m.p. 224° and 9.89 g., m.p. 220°).

Example 83

α - Benzyl - 4(5) - imidazolylacetonitrile

An aqueous solution of 5N sodium hydroxide (10 ml.) was added to a solution of benzaldehyde (15 g.) and 4(5) - cyanomethylimidazole (10 g.) in methanol (100 ml.). After standing at room temperature for 24 hours the reaction mixture was poured into an equal volume of water to give α - benzylidene - 4(5) - imidazolylacetonitrile (14.04 g.) m.p. 189—190°. An analytical sample, recrystallised from ethanol, had m.p. 190—191°.

Powdered sodium amalgam (5%, 240 g.) was added in small portions over 15—20 minutes at room temperature to a vigorously stirred solution of this unsaturated nitrile (6.7 g.) in a mixture of methanol (360 ml.) and water (120 ml.) through which carbon dioxide was passed. After addition, carbon dioxide was passed through the stirred mixture for a further 2½ hours, the solution then decanted from the mercury, filtered and the residue washed with methanol. Evaporation of the filtrate gave an oil which solidified on the addition of water to give α - benzyl - 4(5) - imidazolylacetonitrile (5 g., m.p. 105—107°). An analytical sample, recrystallised from ethanol/water, had m.p. 108.5—110°.

Example 84

4(5) - (1 - Benzyl - 2 - aminoethyl)imidazole dimaleate

(a) To a stirred, cooled mixture of finely ground sodium borohydride (1.3 g.) and a solution of α - benzyl - 4(5) - imidazolylacetonitrile (1 g.) in diglyme (20 ml., dried over mol. sieves) was added dropwise a solution of boron trifluoride monoetherate (5.7 g.) in diglyme (20 ml.) over 30 minutes. After addition, the mixture was stirred for 3 hours and left to stand overnight. Removal of the diglyme at 40°/0.5 mm. gave a residue which was dissolved in methanol, acidified with concentrated hydrochloric acid, and then basified with potassium hydroxide. After heating under reflux for 30 minutes, the mixture was acidified with concentrated hydrochloric acid, evaporated to dryness and the residue extracted with hot dry ethanol. The ethanol extracts were evaporated to dryness and the oily hydrochloride converted to the base by the addition of aqueous potassium carbonate solution. This solution was extracted five times with chloroform, the extracts dried ($MgSO_4$) and the solution evaporated to dryness to give a residue which was dissolved in methanol. Addition of a solution of maleic acid (4 g.) in methanol followed by ether gave an oily solid which was recrystallised from isopropanol/ether to give 4(5) - (1 - benzyl - 2 - aminoethyl)imidazole dimaleate m.p. 145—147°.

(b) A solution of α - benzyl - 4(5) - imidazolylacetonitrile (1 g.) in dry tetrahydrofuran (60 ml.) was added dropwise at room temperature to a stirred suspension of lithium aluminium hydride (0.77 g.) in dried tetrahydrofuran (20 ml.). After addition the mixture was heated under reflux for 2 hours, cooled and excess lithium aluminium hydride destroyed by the addition of water. The mix-

ture was then filtered, the residue washed first with tetrahydrofuran and ethanol and the filtrate evaporated to dryness. A solution of the residual oil in methanol was added to a solution of maleic acid (4 g) in methanol. Addition of ether gave an oily solid which was recrystallised from isopropanol/ether to give 4(5) - (1 - benzyl - 2 - aminoethyl)imidazole dimaleate (0.76 g.), m.p. 146—148°.

Example 85

4(5) - (3 - Benzylaminopropyl)imidazole dihydrochloride

A mixture of 4(5) - (3 - aminopropyl)-imidazole (9 g.) and benzaldehyde (7 ml.) was heated for 2 hours on a steam bath. The reaction mixture was then evaporated to dryness, the residue dissolved in ethanol (90 ml.), and sodium borohydride (5.4 g.) added. After heating under reflux with stirring for 2 hours, excess sodium borohydride was destroyed by the addition of water (15 ml.), and the mixture acidified to pH 1 with concentrated hydrochloric acid. The solution was then basified with aqueous potassium hydroxide and heated under reflux for 30 minutes. After cooling the solution was reacidified with concentrated hydrochloric acid, evaporated to dryness and the residue extracted with hot ethanol (3×50 ml.). The combined extracts were concentrated and ether added to give crude 4(5) - (3 - benzylaminopropyl)imidazole dihydrochloride, which gave pure material (12.4 g.), m.p. 170.5—172°, after recrystallisation from isopropanol.

Example 86

4(5) - (3(3,4 - Dihydroxybenzylamino)propyl)-imidazole dihydrochloride

A solution of protocatechuic aldehyde (11 g.) in ethanol (50 ml.) was added rapidly with stirring to a solution of 4(5) - (3 - aminopropyl)imidazole (10 g.) in ethanol (50 ml.). Sodium borohydride (12.1 g.) was then added cautiously with stirring to the resulting red solution, and the mixture heated under reflux for 2 hours. After cooling the reaction mixture was worked up according to the procedure described in Example 85 to give, after recrystallisation from isopropanol/methanol, pure 4(5) - (3 - (3,4 - dihydroxybenzylamino)-propyl)imidazole dihydrochloride, m.p. 202.5—4°.

Example 87

4(5) - (2 - (3,4 - dihydroxybenzylamino)-ethyl)imidazole dihydrochloride

Histamine (8.9 g.) was reacted with protocatechuic aldehyde (11 g.) and sodium borohydride (12.1 g) using the procedure described in Example 86. The crude dihydrochloride was extracted from inorganic material with a mixture of ethanol and methanol, and a solution of picric acid in ethanol added. The precipitate was recrystallised from methanol/dimethylformamide to give 4(5) - (2 - (3,4 - dihydroxybenzylamino)ethyl)-imidazole dipicrate, m.p. 205—206°. Treatment of this picrate with hydrochloric acid followed by extraction with toluene in the usual way gave the dihydrochloride m.p. 210—212°, after recrystallisation from ethanol/methanol.

Example 88

Preparation of 2 - methyl - 4(5) - (3 - aminopropyl)imidazole dihydrochloride

(i) A hot solution of 1 - bromo - 5 - phthalimidopentan - 2 - one (31.0 g.) in dry ethanol (500 ml.) and dimethylformamide (100 ml.) was added over 3 hours to a solution prepared from acetamidine hydrochloride (28.9 g.) and sodium ethoxide (from sodium, 6.9 g.) in dry ethanol (800 ml.). After addition the mixture was heated under reflux for 2 hours and then allowed to cool. Following filtration and concentration under reduced pressure, the residue was dissolved in ethanol and acidified with a solution of hydrogen chloride in ethanol. The solution was filtered, concentrated and carefully diluted with ethyl acetate. The solid obtained was recrystallised from ethanol - ethyl acetate to give 2 - methyl - 4(5) - (3 - phthalimidopropyl)imidazole hydrochloride, m.p. 216—217°. An analytically pure sample, m.p. 234—236° was obtained by further recrystallisation. The addition of aqueous potassium carbonate liberated the base, m.p. 157—159. Hydrolysis of 2 - methyl - 4(5) - (3 - phthalimidopropyl)-imidazole (4.95 g.) with 5N hydrochloric acid gave 2 - methyl - 4(5) - (3 - aminopropyl)-imidazole dihydrochloride (2.96 g.) m.p. 188—192°. An analytically pure sample, obtained by recrystallisation from ethanol - ether, had m.p. 193—195°.

Example 89

Preparation of 1 - Methyl - 4(5) - (3 - aminopropyl)imidazole dihydrochloride

(i) A mixture of 4(5) - (3 - aminopropyl)-imidazole (16 g.) and acetic anhydride (30 ml.) was heated under reflux for 1 hour. After cooling, water (60 ml.) was added and the solution concentrated to dryness under reduced pressure. A further quantity of water (60 ml.) was added to the residual oil and the mixture evaporated to dryness to give the N - acetyl derivative as an oil which was not purified further. Dimethyl sulphate (7.6 ml.) was then added dropwise to a stirred solution of this crude oil in 10% aqueous sodium hydroxide (100 ml.) during which time the temperature was maintained between 20—30°C. After the addition, further quantities of sodium hydroxide (100 ml.) and dimethyl sulphate (7.6 ml.) were added as before and finally the solution was heated for 45 minutes on a steam bath. After cooling, the solution was saturated with sodium sulphate, extracted with chloro-

form (9×100 ml.), and the chloroform extracts evaporated to dryness. The residue was dissolved in 6N hydrochloric acid (300 ml.), and the solution heated under reflux overnight. Evaporation to dryness gave an oily residual hydrochloride, which was dissolved in water and converted into the picrate by the addition of an ethanolic solution of picric acid. The crude picrate obtained (33.3 g.) was recrystallised three times from ethamel - water to give the isomerically pure dipicrate (16.4 g.), m.p. 190—191°. (An analytically pure sample had m.p. 194—196°). 1 - Methyl - 4 - (5) - (3 - aminopropyl)imidazole dihydrochloride (4.8 g., m.p. 254—256) was obtained from the dipicrate in the usual way with hydrochloric acid. Recrystallisation of the dihydrochloride from methanol/ether gave a pure sample m.p. 258—259°.

Example 90

N - (2 - (4 - Imidazolyl)ethyl) - N' - (2 - aminoethyl)urea

Ethylenediamine (80 ml.) was added dropwise over 15 minutes to a stirred suspension of 5 - oxo - 5,6,7,8 - tetrahydroimidazo(1,5 - c)pyrimidine (15 g.) in ethanol (250 ml.) at room temperature. After addition the mixture was stirred overnight and then evaporated to dryness to give N - (2 - (4 - imidazolyl)-ethyl) - N' - (2 - aminoethyl)urea (19.9 g.), m.p. 112—116°. The dimaleate (ex ethanol/isopropanol) had m.p. 120—122°.

Example 91

N - (2 - (4(5) - imidazolyl)ethyl)glycine hydrochloride

5 - Oxo - 6 - (2 - ethoxycarbonylmethyl) - 5,6,7,8 - tetrahydroimidazo(1,5 - c)pyrimidine (2.63 g.) was added to a solution of lithium hydroxide (1.5 g.) in water (15 ml.) and the mixture heated under reflux for 21 hours. After cooling, the mixture was filtered, and concentrated to half volume, and acidified with hydrochloric acid. After evaporation to dryness, the solid residue was extracted with n - butanol and filtered to give the crude product (1.78 g.), m.p. 245—255°. Recrystallisation from methanol gave pure N - (2 - (4(5) - imidazolyl)ethyl)glycine as a non-stoichiometric hydrochloride, m.p. 235—239°.

Example 92

4(5) - (2 - (Cyanomethylamino)ethyl)imidazole dihydrochloride

A solution of histamine (30 g.) in methanol (200 ml.) was added to a solution of glycollonitrile (70%, 22 g.) in methanol (20 ml.). The mixture was stirred at room temperature for 4 days and then evaporated to dryness. The residual oil was dissolved in dry ethanol and acidified with ethanolic hydrogen chloride to give an oily solid, which was recrystallised from ethanol/isopropanol to give 4(5) - (2 - (cyanomethylamino)ethyl)imidazole dihydrochloride (39.8 g.), m.p. 152—154° (dec.). An analytical sample had m.p. 155—156°.

Example 93

2 - (4(5) - Imidazolyl ethyl)amino acetamidine

A solution of 4(5) - (2 - (cyanomethylamino)ethyl)imidazole dihydrochloride (20 g.) in methanol (350 ml., dried over molecular sieves) was added dropwise over 10 minutes to a solution of dry hydrogen chloride gas (214 g.) in methanol (350 ml.) at −10°. After addition the mixture was stirred at 0—6° for 3 hours, poured into excess anhydrous ether and the precipitated iminoether hydrochloride collected and used directly in the next experiment.

The above iminoether hydrochloride was added portionwise to a saturated solution of ammonia (~32 g.) in ethanol (150 ml., dried over molecular sieves, cooled to −1°. The mixture was then stirred between 0—6° for 2½ hours, allowed to warm up to room temperature, and filtered. The filtrate was evaporated to dryness under reduced pressure using a water bath maintained at 40°. The residual oil was dissolved in ethanol and a hot solution of excess picric acid in ethanol added. After cooling the crystals were collected to give 2 - (4(5) - Imidazolylethyl)-amino acetamidine tripicrate (52.7 g.), m.p. 191—192° (dec.). An analytical sample (m.p. 191—192°) was recrystallised from nitromethane/ethanol.

Treatment of this picrate with hydrochloric acid followed by extraction with toluene in the usual way gave a crude hydrochloride salt, which was washed with a mixture of methanol and dimethylformamide and then recrystallised from methanol/water to give the pure trihydrochloride, m.p. 214—217° (dec.).

Example 94

4(5) - (2 - (Di - (2 - hydroxyethyl)amino)-ethyl)imidazole

A solution of 4(5) - (2 - bromoethyl)-imdiazole hydrobromide (20 g.) in diethanolamine (150 g.) was heated on a steam bath overnight. The solution was then evaporated to dryness, a solution of potassium carbonate (10.8 g.) in water (50 ml.) was added and the mixture evaporated to dryness. The last traces of diethanolamine were removed by shaking with benzene. The oily product was dissolved in ethanol, the solution filtered and the filtrate acidified with ethanolic hydrogen chloride to give 4(5) - (2 - (Di - (2 - hydroxyethyl)-amino)ethyl)imidazole dihydrochloride m.p. 114—118°, on addition of isopropanol.

Addition of ethanolic hydrogen bromide to the base gave the dihydrobromide salt, m.p. 141—144°, after recrystallisation from isopropanol/ethanol.

Example 95

4(5) - (2(N,N - bis(2 - chloroethyl)amino)-ethyl)imidazole dihydrochloride

4(5) - (2 - (Di - (2 - hydroxyethyl)amino)-ethyl)imidazole dihydrochloride (2 g.) was added portionwise with stirring to thionyl chloride (25 ml.). After addition the mixture was heated on a steam bath for 15 minutes and then evaporated to dryness under reduced pressure. After removal of final traces of thionyl chloride by azeotroping with benzene the residual oil was dissolved in isopropanol, charcoaled, and the solution left to stand at —10°. The crystals were filtered off to give the required dihydrochloride (1.56 g.), m.p. 147—148°.

Example 96

4 - (2 - N - (2 - Bromoethyl) - N - methyl)-aminoethyl)imidazole dihydrobromide

A solution of 4(5) - (2 - (N - (2 - hydroxyethyl) - N - methyl)aminoethyl)imidazole dihydrochloride in hydrobromic acid (48%, 50 ml.) and hydriodic acid (2 drops) was heated under reflux for 4 days. After cooling the solution was evaporated to dryness, the residue dissolved in a minimum of dry ethanol, and after cooling, the required dihydribromide (2.7 g.), m.p. 182—185° was filtered off. An analytical sample, recrystallised from ethanol, had m.p. 187—189°.

Example 97

4 - (2 - (N - (2 - Chloroethyl) - N - methyl)-aminoethyl)imidazole dihydrochloride

Reaction of 4(5) - (2 - (N - (2 - hydroxyethyl) - N - methyl)aminoethyl)imidazole dihydrochloride (2.42 g.) with thionyl chloride by the method described in Example 95 gave 4 - (2 - (N - (2 - chloroethyl) - N - methyl)-aminoethyl)imidazole dihydrochloride (1.62 g.), m.p. 192—195°, after recrystallisation of the crude product from ethanol.

Example 98

4 - (2 - (N - (2 - Bromoethyl))aminoethyl)-imidazole dihydrobromide

4 - (2 - (N - (2 - Hydroxyethyl))amino-ethyl)imidazole dipicrate (32 g.) was converted to the dihydrobromide by treatment with aqueous hydrobromic acid (5N) and extraction with toluene in the usual way. After evaporation of the aqueous phase the residue was reacted with 48% hydrobromic acid by the method described in Example 96 to give 4 - (2 - (N - (2 - bromoethyl))aminoethyl)-imidazole dihydrobromide (6 g.), m.p. 136—138°, after recrystallisation of the crude product from methanol/isopropanol.

Example 99

4(5) - (3 - (N - (2 - Hydroxyethyl) - N - methyl)aminopropyl)imidazole dipicrate

Reaction of 4(5) - (3 - chloropropyl)-imidazole hydrochloride (5.2 g.) with N - methylethanolamine (50 ml.) by the method described in Example 94 gave the required dipicrate (12.1 g.), m.p. 147—149°, after recrystallisation from nitromethane.

Example 100

4(5) - (3 - (N - (2 - bromoethyl) - N - methyl)aminopropyl)imidazole dihydrobromide

4(5) - (3 - (N - (2 - Hydroxyethyl) - N - methyl)aminopropyl)imidazole dipicrate (7 g.) was converted to the corresponding dihydrobromide and then reacted with 48% hydrobromic acid (150 ml.) by the method described in Example 96 to give 4(5) - (3 - (N - (2 - bromoethyl) - N - methyl)aminopropyl)-imidazole dihydrobromide (3.87 g.), m.p. 195—197°, after recrystallisation from ethanol.

Example 101

4(5) - (3 - (N - (2 - chloroethyl) - N - methyl)aminopropyl)imidazole dihydrochloride

4(5) - (3 - (N - (2 - Hydroxyethyl) - N - methyl)aminopropyl)imidazole dipicrate (4 g.) was treated with 5N hydrochloric acid and extracted with toluene in the usual way. The aqueous phase was evaporated to dryness and the residual oil reacted with thionyl chloride (15 ml.), by the method described in Example 95, to give 4(5) - (3 - (N - (2 - chloroethyl) - N - methyl)aminopropyl)imidazole dihydrochloride (1 g.), m.p. 158—160°, after recrystallisation from isopropanol.

WHAT WE CLAIM IS:—

1. Aminoalkylimidazoles of the formula:

wherein A is a saturated straight chain of from 1 to 6 carbon atoms, which chain may be substituted by one or more alkyl or aralkyl groups; R is a substituted or unsubstituted alkyl, aryl or aralkyl group; R_1 is hydrogen, alkylphenyl, phenylalkyl or imidazolylalkyl; R_{20} is hydrogen, alkyl optionally substituted by halogen, hydroxy, cyano, carboxy, amino or amidino, or —COY wherein Y is $R_{11}O$ or $R_{11}NH$ and R_{11} is a substituted or unsubstituted alkyl, aryl or aralkyl group or an amidine group; and X is 0, 1, 2 or 3 provided that, when X is 0 and R_{20} is hydrogen or an alkyl group containing from 1 to 3 carbon atoms, R_1 may not be hydrogen, benzyl or an alkyl group containing from 1 to 3 carbon atoms and that when R_1 and R_{20} are both hydrogen or alkyl, A is a saturated straight chain of 2 carbon atoms optionally substituted by methyl and X is 1, R may not be methyl, or, except when substituted in the 4(5) position of the ring, phenyl or benzyl.

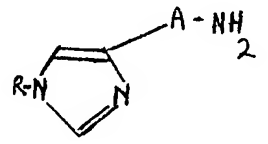
2. Aminoalkylimidazoles according to claim 1 wherein X is 0 and R_{20} is hydrogen.

3. Aminoalkylimidazoles according to claim 1 wherein R_{20} is a substituted alkyl group of

the formula $-(CH_2)_nZ$ wherein n is 1, 2 or 3 and Z is halogen, cyano, carboxy, hydroxy, amino or amidino.

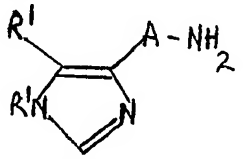
4. Aminoalkylimidazoles according to claim 3 wherein X is 0, R_1 is methyl and R_{20} is 2 - chloroethyl or 2 - bromethyl.

5. Aminoalkylimidazoles according to claim 1 of the general formula:



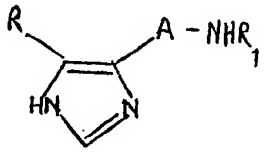
wherein R and A have the same significance as in claim 1.

6. Aminoalkylimidazoles according to claim 1 of the general formula



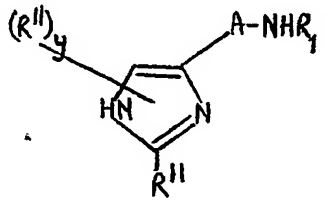
wherein each R^1 is a methyl or a benzyl group, and A has the same significance as in claim 1.

7. Aminoalkylimidazoles according to claim 1 of the general formula



wherein A, R and R_1 have the same significance as in claim 1.

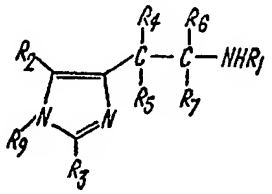
8. Aminoalkylimidazoles according to claim 1 of the general formula



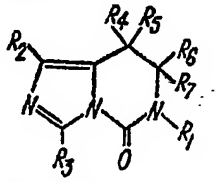
wherein R^{11} is a substituted or unsubstituted aryl or aralkyl, y is 0, 1 or 2, and A and R_1 have the same significance as in claim 1.

9. Pharmaceutical compositions comprising an aminoalkylimidazole according to any one of the preceding claims and claim 35 together with a pharmaceutically acceptable diluent or carrier.

10. A method for the production of compounds according to claim 1 and of the general formula



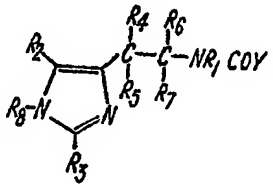
wherein R_1 has the same significance as in the formula of claim 1; R_2 and R_3 are hydrogen or substituted or unsubstituted alkyl, aryl or aralkyl; R_4, R_5, R_6 and R_7 are hydrogen, alkyl or aralkyl and R_9 is alkyl, aminoalkyl, carboxyalkyl or substituted or unsubstituted aryl or aralkyl, provided that, when R_1, R_2 and R_3 are all hydrogen and one of R_4, R_5, R_6 and R_7 is hydrogen or methyl when the others of R_4, R_5, R_6 and R_7 are hydrogen, R_9 may not be methyl, phenyl or benzyl, in which a compound of the formula



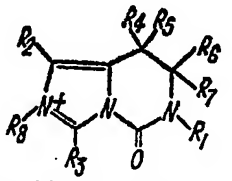
is reacted with a compound of formula R_8X wherein R_8 is a group which is identical with R_9 or which on hydrolysis is converted to R_9 and X is halogen and the product of this reaction is then hydrolysed.

11. A method according to claim 10 wherein R_1, R_3, R_4, R_5, R_6 and R_7 are hydrogen.

12. A method for the production of a compound according to claim 1 and of the formula



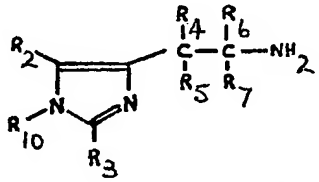
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 have the same significance as in the formulae set out in claim 10 and additionally R_8 may be hydrogen; Y is $R_{11}NH$ or $R_{11}O$ wherein R_{11} is a substituted or unsubstituted alkyl, aryl or aralkyl group or an amidine group; and Z^- is a suitable anion in which a compound of formula



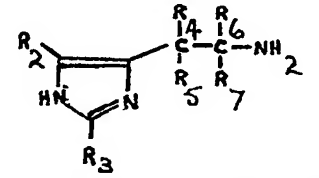
is reacted with a nucleophilic reagent of formula YH.

13. A method according to claim 12 in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are all hydrogen, R_8 is hydrogen or benzyl and Y is methoxy, guanidine, 2 - aminoethylamino or substituted or unsubstituted 2 - (4(5) - imidazolyl)ethylamino.

14. A method for the production of compounds according to claim 1 and of the general formula



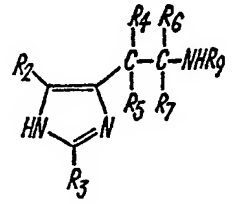
wherein R_2, R_3, R_4, R_5, R_6 and R_7 have the same significance as in the formula set out in claim 10 and R_{10} is a substituted or unsubstituted aralkyl group provided that, when R_2 and R_3 are both hydrogen and one of R_4, R_5, R_6 and R_7 is hydrogen or methyl when the others of R_4, R_5, R_6 and R_7 are hydrogen, R_{10} may not be benzyl in which a compound of the formula



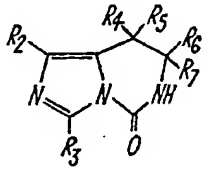
is converted by treatment with N - carbethoxyphthalimide to the corresponding phthalimido compound which compound is then reacted with a substance of formula $R_{10}X$ wherein X is halogen and the product of that reaction is hydrolysed to remove the phthalimido group.

15. A method according to claim 14 wherein R_2, R_3, R_4, R_5, R_6 and R_7 are hydrogen and R_{10} is phenylethyl.

16. A method for the production of a compound according to claim 1 and of the formula



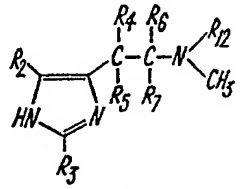
wherein R_2 and R_3 are hydrogen or substituted or unsubstituted alkyl, aryl, or aralkyl; R_4, R_5, R_6 and R_7 are hydrogen, alkyl or aralkyl and R_9 is alkyl, aminoalkyl, carboxyalkyl, phenyl, phenylalkyl or imidazolylalkyl; provided that, when R_2 and R_3 are hydrogen, R_9 may not be an alkyl group containing from 1 to 3 carbon atoms or benzyl, in which a compound of the formula



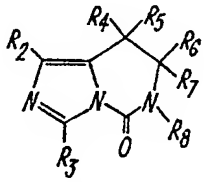
is treated with a base and then with R_9X wherein R_9 is group which is identical with R_9 or which on hydrolysis is converted to R_9 and X is halogen, the product of the latter reaction being then hydrolysed.

17. A method according to claim 16 wherein R_3, R_4, R_5, R_6 and R_7 are hydrogen; R_2 is hydrogen, alkyl or phenylalkyl and R_9 is alkyl, phenylalkyl or carbethoxymethyl.

18. A method for the production of a compound according to claim 1 and of the formula



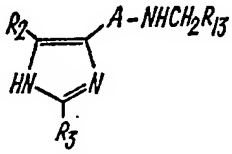
wherein R_2, R_3, R_4, R_5, R_6 and R_7 have the same significance as in the formula set out in claim 16 and R_{12} either has the same significance as R_8 in that formula or is the reduction product of R_8 in which a compound of the formula



is treated with lithium aluminium hydride to cleave the pyrimidine ring and form the N - methyl group.

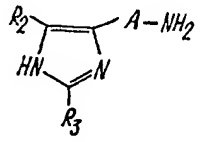
19. A method according to claim 18 wherein R_3, R_4, R_5, R_6 and R_7 are hydrogen, R_2 is hydrogen or methyl and R_{12} is 2-hydroxyethyl or phenylalkyl.

20. A method for the production of a compound according to claim 1 and of the formula



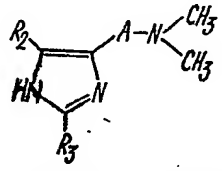
wherein A has the same significance as in the formula set out in claim 1; R_2 and R_3 are hydrogen or substituted or unsubstituted alkyl, aryl or aralkyl; and R_{13} is hydrogen,

alkyl, phenyl, phenylalkyl or imidazolylalkyl provided that, when R_2 and R_3 ar both hydrogen, R_{13} may not be hydrogen, methyl, ethyl or phenyl, in which a compound of the formula

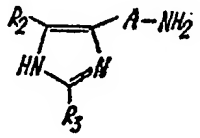


is treated with an acyl compound of the formula $(R_{13}CO)_2O$ or $R_{13}COX$ where X is halogen and the resultant product is reacted with lithium aluminium hydride to reduce the carbonyl group of the intermediate amide to a methylene group.

21. A method for the production of a compound according to claim 1 and of the formula

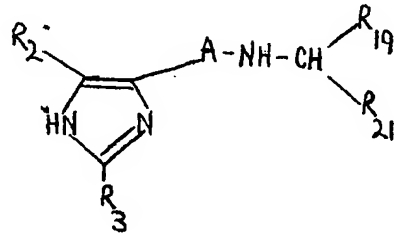


wherein R_2 and R_3 are hydrogen or substituted alkyl, aryl or aralkyl; and A has the same significance as in the formula set out in claim 1, provided that when R_3 is hydrogen, R_2 may not be hydrogen or methyl, and when A represents a chain of 2 carbon atoms, R_2 may not be hydrogen, in which a compound of the formula:

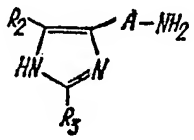


is treated with formic acid and formaldehyde.

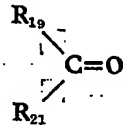
22. A method for the production of a compound according to claim 1 and of the formula



wherein R_2 and R_3 are hydrogen or substituted or unsubstituted alkyl, aryl or aralkyl; A has the same significance as in the formula set out in claim 1; and R_{19} and R_{21} are hydrogen, alkyl, phenyl, phenylalkyl or imidazolylalkyl, provided that R_{19} and R_{21} may not both be phenyl, phenylalkyl or imidazolylalkyl and that, when R_2 and R_3 are both hydrogen, $CHR_{19}R_{21}$ may not be benzyl or an alkyl group containing from 1 to 3 carbon atoms and when R_{19} and R_{21} are both hydrogen or alkyl, A is a saturated straight chain of 2 carbon atoms optionally substituted by methyl and one of R_2 and R_3 is hydrogen, R_2 may not be methyl and R_3 may not be methyl, phenyl or benzyl, in which a compound of the formula



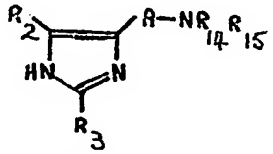
is reacted to form a Schiff's base with a carbonyl compound of formula



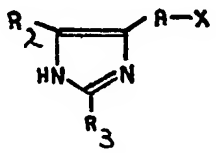
and the Schiff's base is then reduced.

23. A method according to claim 22 wherein R_2 and R_3 are hydrogen, R_{19} is hydrogen or methyl and R_{21} is phenylalkyl.

24. A method for the production of a compound according to claim 1 and of the formula



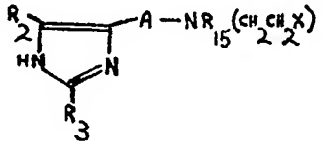
wherein R_2, R_3 and A have the same significance as in the formula set out in claim 22; R_{14} is alkyl optionally substituted by halogen, hydroxy, cyano, carboxy, amino or amidino; and R_{15} is hydrogen, alkyl, phenyl, phenylalkyl or imidazolylalkyl, provided that when R_2 and R_3 are both hydrogen, R_{15} may not be hydrogen, an alkyl group containing from 1 to 6 carbon atoms or benzyl and, when R_{14} and R_{15} are both alkyl, A is a saturated straight chain of 2 carbon atoms optionally substituted by methyl and one of R_2 and R_3 is hydrogen, R_2 may not be methyl and R_3 may not be methyl, phenyl or benzyl in which a compound of formula



wherein X is halogen is reacted with an amine of formula $R_{14}R_{15}NH$.

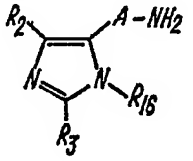
25. A method according to claim 24 wherein R_2 and R_3 are hydrogen, R_{14} is methyl or 2 - hydroxyethyl and R_{15} is hydrogen, 2 - hydroxyethyl 2 - aminoethyl or phenylalkyl.

26. A method for the production of a compound according to claim 1 and of the formula,

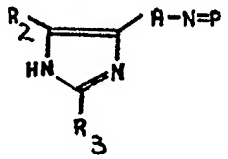


wherein A, R_2, R_3 and R_{15} have the same significance as in the formula set out in claim 24 and X is chloro or bromo from a compound of the said formula wherein X is hydroxy.

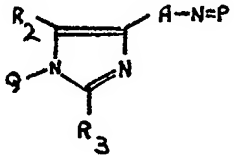
27. A method for the production of a compound of the formula



wherein A, R_2 and R_3 have the same significance as in the formulae set out in claim 20 and R_{16} is a substituted or unsubstituted alkyl or aralkyl group provided that, when R_2 and R_3 are both hydrogen and A is a saturated straight chain of two carbon atoms optionally substituted by methyl, R_{16} may not be methyl, phenyl or benzyl, in which a compound of the formula

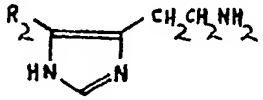


wherein P is a phthalimido group is reacted with a pivaloyloxymethyl halide to give a compound of the formula

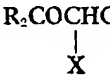


wherein Q is pivaloyloxymethyl and then reacted with a substance of the formula $R_{16}X$ wherein X is halogen, the protective phthalimido and pivaloyloxymethyl groupings then being removed by hydrazinolysis to give the required compound.

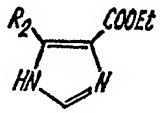
28. A method for the production of histamine derivatives according to claim 1 and of the formula



wherein R_2 is substituted or unsubstituted alkyl other than methyl or is a substituted or unsubstituted aryl or aralkyl other than phenyl or benzyl in which a compound of formula



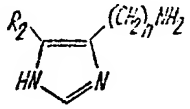
wherein X is halogen or amino, is reacted with formamide to produce a compound of the formula



which is then converted to the desired histamine derivative by way the corresponding hydroxymethyl, halomethyl and cyanomethyl imidazoles.

29. A method according to claim 28 wherein R_2 is isopropyl or t-butyl.

30. A method for the production of a compound according to claim 1 and of the formula



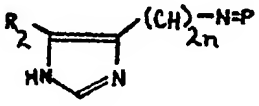
wherein R_2 has the same significance as in the formula set out in claim 28, and n is from 1 to 6 in which a compound of the formula

$$R_2C{\equiv}C—A—N:P$$

wherein P is a phthalimido group is oxidised to a substance of formula

$$R_2COCO—A—N:P$$

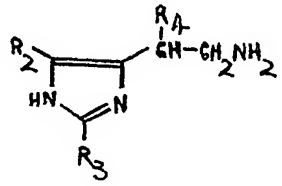
which substance is then reacted with formaldehyde and ammonium acetate to give a compound of the formula



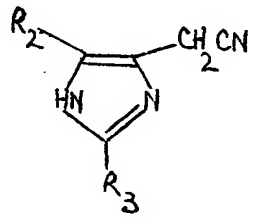
which is then hydrolysed to give the required compound.

31. A method according to claim 30 in which R_2 is ethyl, n-hexyl or phenylpropyl.

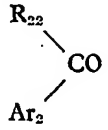
32. A method for the production of a compound according to claim 1 and of the formula



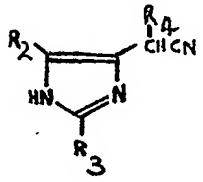
wherein R_2 and R_3 are hydrogen or substituted or unsubstituted alkyl, aryl or aralkyl and R_4 is substituted or unsubstituted arylmethyl, provided that R_2 and R_3 may not both be hydrogen, in which a compound of the formula



is reacted with a carbonyl compound of formula



wherein R_{22} is hydrogen or alkyl and Ar_2 is substituted or unsubstituted aryl and the resultant product is first reduced to give a substance of the formula



which product is then further reduced to the required compound.

33. A method for the production of aminoalkylimidazoles according to claim 1 as hereinbefore described in any one of the examples 6—12, 15, 16, 18, 20, 21, 23, 28—36, 39, 41, 48—53 and 58—67.

34. A method for the production of aminoalkylimidazoles according to claim 1 as hereinbefore described in any one of examples 70—72, 74, 75, 77—79, 81—83, 87, 88 and 92—104.

35. Aminoalkylimidazoles according to claim 1 whenever produced by a process according to any one of claims 10 to 34.

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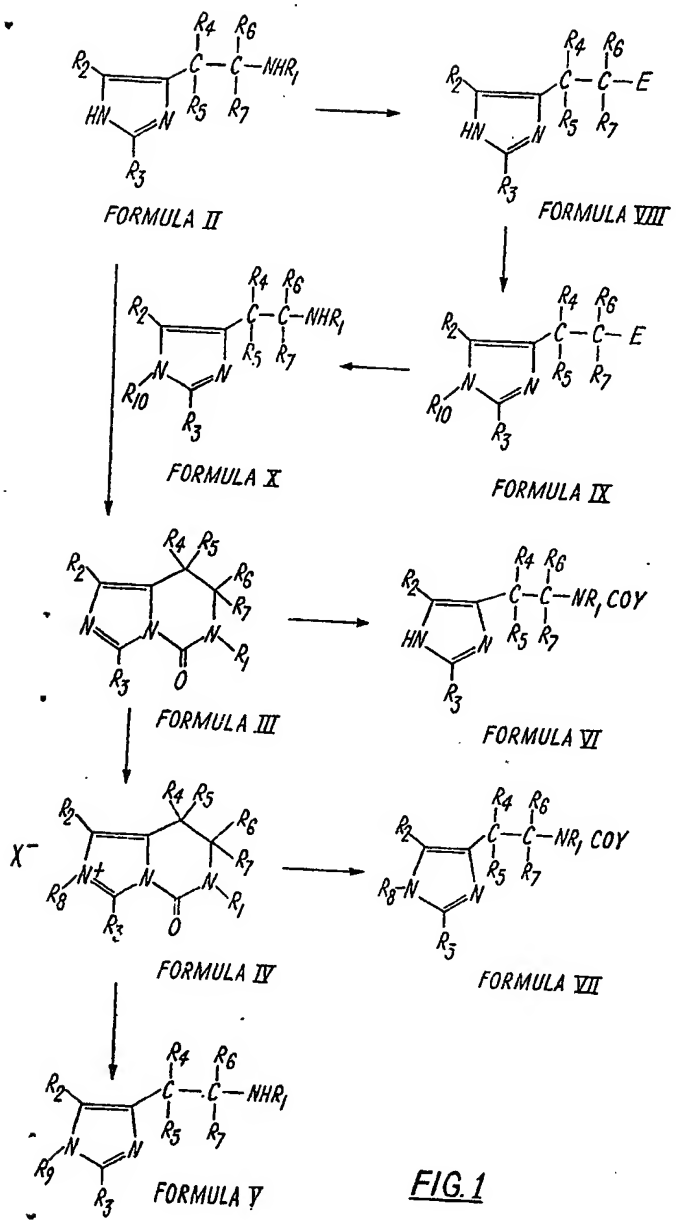

FORMULA II
FORMULA VIII
FORMULA IX
FORMULA X
FORMULA III
FORMULA VI
FORMULA IV
FORMULA VII
FORMULA V

FIG. 1

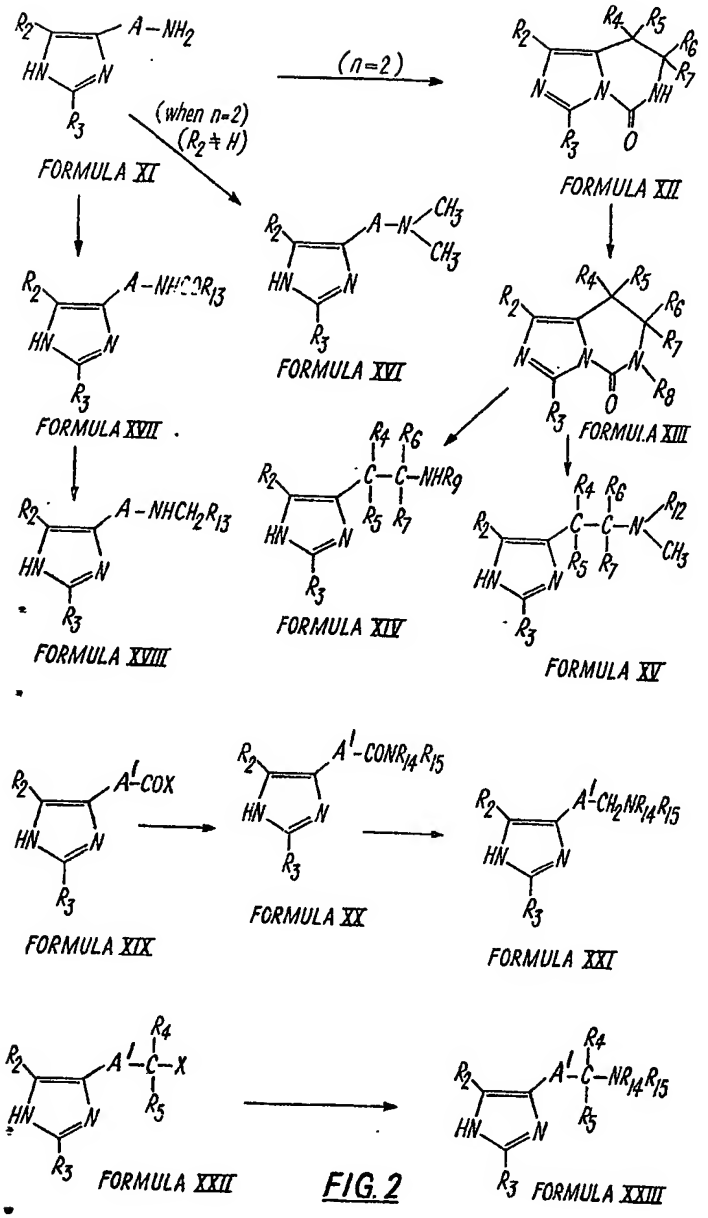

(n=2)
(when n=2)
(R2 ≠ H)
FORMULA XI
FORMULA XII
FORMULA XIII
FORMULA XIV
FORMULA XV
FORMULA XVI
FORMULA XVII
FORMULA XVIII
FORMULA XIX
FORMULA XX
FORMULA XXI
FORMULA XXII
FORMULA XXIII

FIG. 2

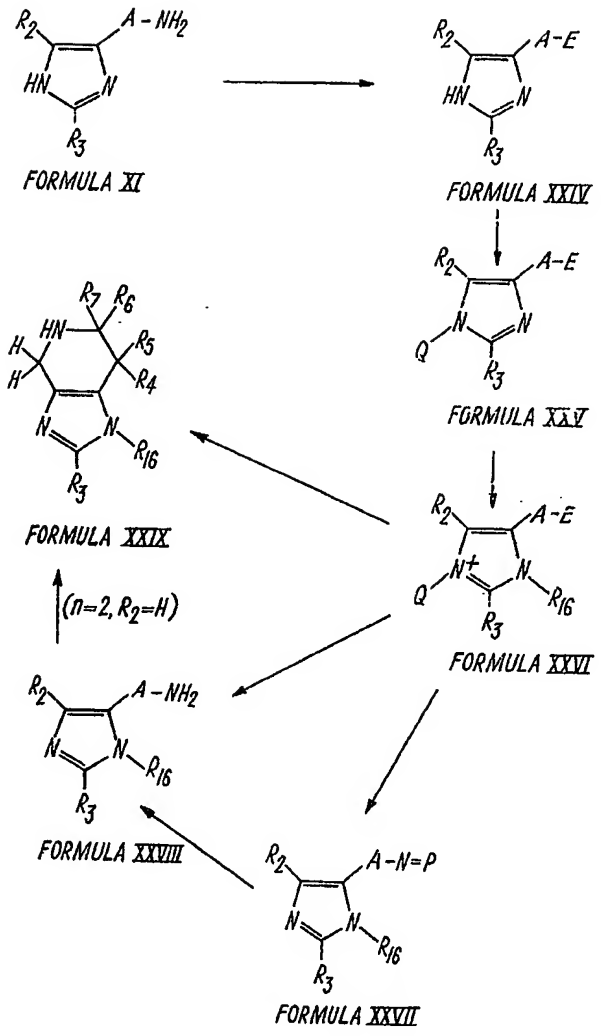

FORMULA XI
FORMULA XXIV
FORMULA XXV
FORMULA XXIX
(n=2, R2=H)
FORMULA XXVI
FORMULA XXVIII
FORMULA XXVII

FIG. 3

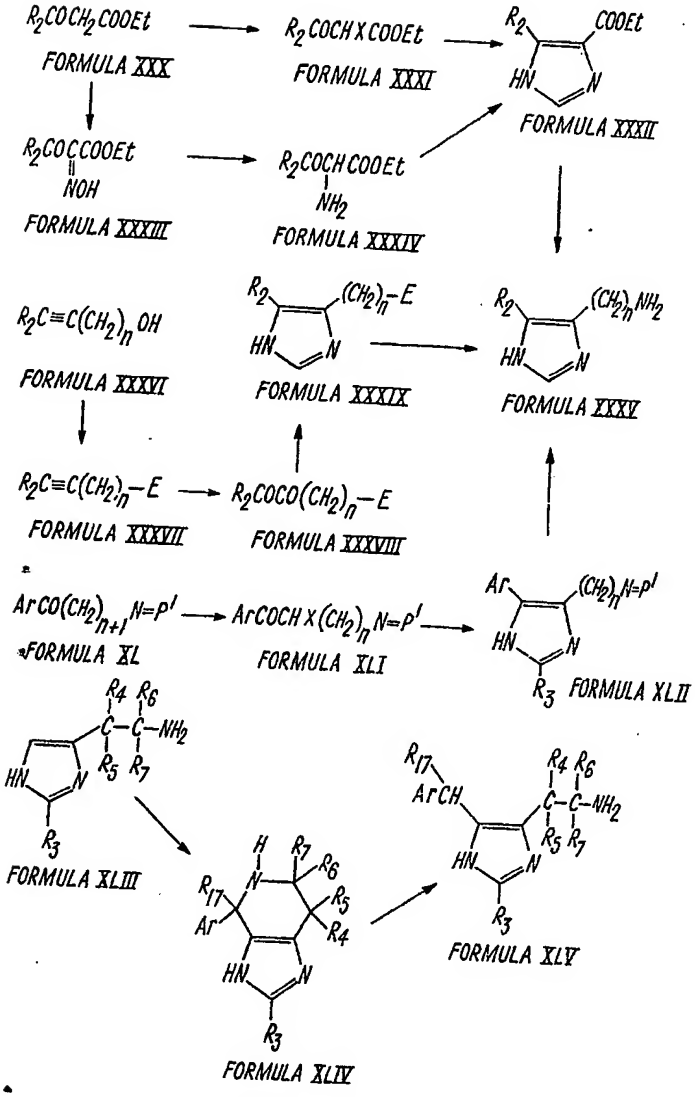

R2COCH2COOEt
FORMULA XXX
R2COCHXCOOEt
FORMULA XXXI
COOEt
FORMULA XXXII
R2COCCOOEt
NOH
FORMULA XXXIII
R2COCHCOOEt
NH2
FORMULA XXXIV
R2C≡C(CH2)nOH
FORMULA XXXVI
(CH2)n-E
FORMULA XXXIX
(CH2)nNH2
FORMULA XXXV
R2C≡C(CH2)n-E
FORMULA XXXVII
R2COCO(CH2)n-E
FORMULA XXXVIII
ArCO(CH2)n+1N=P'
FORMULA XL
ArCOCHX(CH2)nN=P'
FORMULA XLI
(CH2)nN=P'
R3 FORMULA XLII
FORMULA XLIII
FORMULA XLIV
FORMULA XLV

FIG. 4

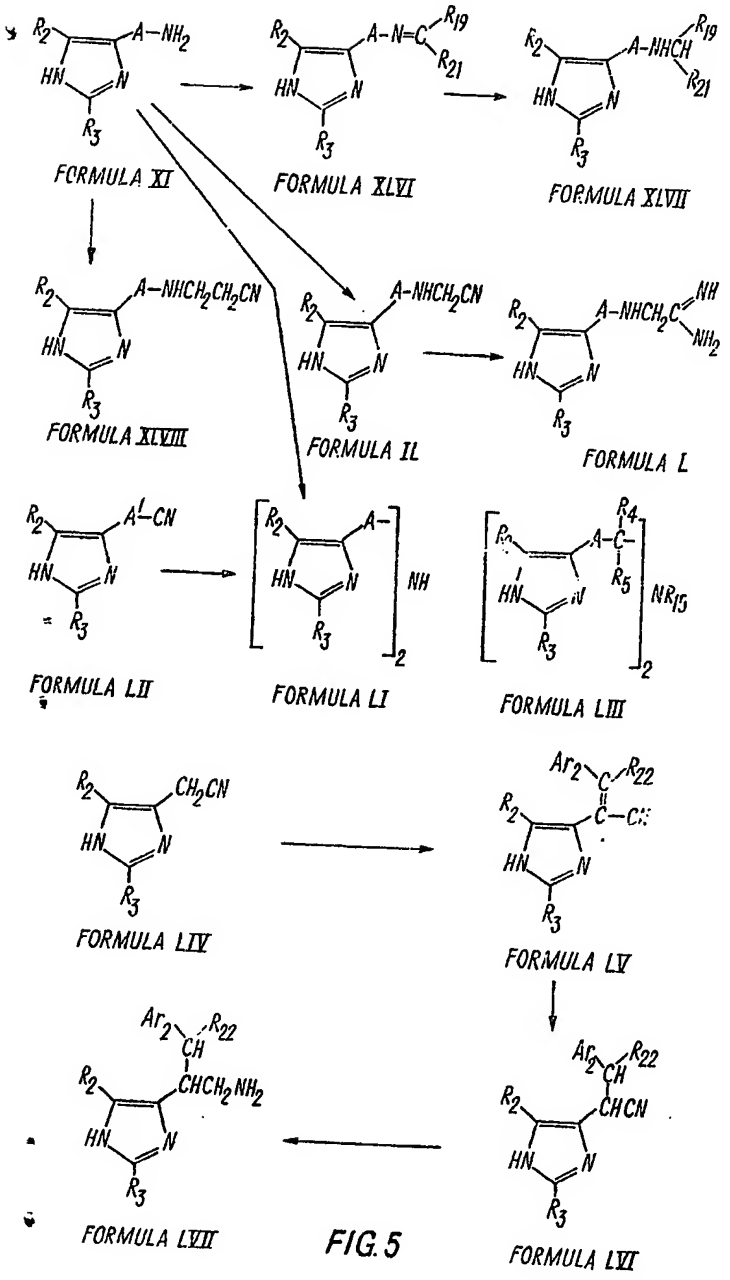
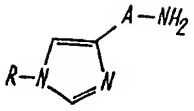

FORMULA XI
FORMULA XLVI
FORMULA XLVII
FORMULA XLVIII
FORMULA IL
FORMULA L
FORMULA LII
FORMULA LI
FORMULA LIII
FORMULA LIV
FORMULA LV
FORMULA LVII
FORMULA LVI

FIG. 5



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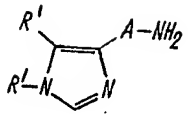

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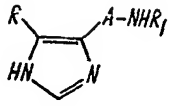
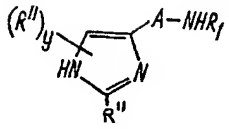


IE



IF

FIG.6